

Exhibit 1

Meeting January 14 1965

The Environment and Disease: Association or Causation?

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Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what *might* a particular environment do to man, and then see whether such consequences are indeed to be found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this

President's Address

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) *Strength*. First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the *enormous* increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times

as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic ‘you can’t prove it, there *may* be such a feature’.

Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute difference between the death rates of our various groups and not the ratio of one to other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (i.e. presuming causation), then obviously we must use the absolute differences between the death rates – 0.07 per 1,000 per year in non-smoking doctors, 0.57 in those smoking 1–14 cigarettes daily, 1.39 for 15–24 cigarettes daily and 2.27 for 25 or more daily. But it does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to aetiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative. It does not, of course, follow that the differences revealed by ratios are of any practical importance. Maybe they are, maybe they are not; but that is another point altogether.

We may recall John Snow’s classic analysis of the opening weeks of the cholera epidemic of 1854 (Snow 1855). The death rate that he recorded in the customers supplied with the grossly polluted water of the Southwark and Vauxhall Company was in truth quite low – 71 deaths in each 10,000 houses. What stands out vividly is the fact that the small rate is 14 times the figure of 5 deaths per 10,000 houses supplied with the sewage-free water of the rival Lambeth Company.

In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on

the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat’s urine contract Weil’s disease.

(2) *Consistency*: Next on my list of features to be specially considered I would place the *consistency* of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

This requirement may be of special importance for those rare hazards singled out in the Section’s terms of reference. With many alert minds at work in industry today many an environmental association may be thrown up. Some of them on the customary tests of statistical significance will appear to be unlikely to be due to chance. Nevertheless whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and the observations.

Returning to my more general example, the Advisory Committee to the Surgeon-General of the United States Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries (US Department of Health, Education & Welfare 1964). The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guard against that.

Take, for instance, an example given by Heady (1958). Patients admitted to hospital for operation for peptic ulcer are questioned about recent domestic anxieties or crises that may have precipitated the acute illness. As controls, patients admitted for operation for a simple hernia are similarly quizzed. But, as Heady points out, the two groups may not be *in pari materia*. If your wife ran off with the lodger last week you still have to take your perforated ulcer to hospital without delay. But with a hernia you might prefer to stay at home for a while – to mourn (or celebrate) the event. No number of exact repetitions would remove or necessarily reveal that fallacy.

We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the

original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively.

Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions. The experience of the nickel refiners of South Wales is an outstanding example. I quote from the Alfred Watson Memorial Lecture that I gave in 1962 to the Institute of Actuaries:

'The population at risk, workers and pensioners, numbered about one thousand. During the ten years 1929 to 1938, sixteen of them had died from cancer of the lung, eleven of them had died from cancer of the nasal sinuses. At the age specific death rates of England and Wales at that time, one might have anticipated one death from cancer of the lung (to compare with the 16), and a fraction of a death from cancer of the nose (to compare with the 11). In all other bodily sites cancer had appeared on the death certificate 11 times and one would have expected it to do so 10-11 times. There had been 67 deaths from all other causes of mortality and over the ten years' period 72 would have been expected at the national death rates. Finally division of the population at risk in relation to their jobs showed that the excess of cancer of the lung and nose had fallen wholly upon the workers employed in the chemical processes.

'More recently my colleague, Dr Richard Doll, has brought this story a stage further. In the nine years 1948 to 1956 there had been, he found, 48 deaths from cancer of the lung and 13 deaths from cancer of the nose. He assessed the numbers expected at normal rates of mortality as, respectively 10 and 0.1.

'In 1923, long before any special hazard had been recognized, certain changes in the refinery took place. No case of cancer of the nose has been observed in any man who first entered the works after that year, and in these men there has been no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century.

'No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any clue or any support to this wholly statistical evidence. Yet I wonder if any of us would hesitate to accept it as proof of a grave industrial hazard?' (Hill 1962).

In relation to my present discussion I know of no parallel investigation. We have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so.

(3) *Specificity*: One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider. If, as here, the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation.

We must not, however, over-emphasize the importance of the characteristic. Even in my present example there is a cause and effect relationship with two different sites of cancer – the lung and the nose. Milk as a carrier of infection and, in that sense, the cause of disease can produce such a disparate galaxy as scarlet fever, diphtheria, tuberculosis, undulant fever, sore throat, dysentery and typhoid fever. Before the discovery of the underlying factor, the bacterial origin of disease, harm would have been done by pushing too firmly the need for specificity as a necessary feature before convicting the dairy.

Coming to modern times the prospective investigations of smoking and cancer of the lung have been criticized for not showing specificity – in other words the death rate of smokers is higher than the death rate of non-smokers from many causes of death (though in fact the results of Doll & Hill, 1964, do not show that). But here surely one must return to my first characteristic, the strength of the association. If other causes of death are raised 10, 20 or even 50% in smokers whereas cancer of the lung is raised 900-1,000% we have specificity – a specificity in the magnitude of the association.

We must also keep in mind that diseases may have more than one cause. It has always been possible to acquire a cancer of the scrotum without sweeping chimneys or taking to mule-spinning in Lancashire. One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor.

In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.

(4) *Temporality*: My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse? This is a question which might be particularly relevant with diseases of slow development. Does a particular diet lead to disease or do the early stages of the disease lead to those peculiar dietetic habits? Does a

particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment – or, indeed, have they already contracted it? This temporal problem may not arise often but it certainly needs to be remembered, particularly with selective factors at work in industry.

(5) *Biological gradient*: Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. That comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause-and-effect hypothesis. The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light.

The same would clearly be true of an alleged dust hazard in industry. The dustier the environment the greater the incidence of disease we would expect to see. Often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose-response. But we should invariably seek it.

(6) *Plausibility*: It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

‘... no biological knowledge to support (or to refute) Pott’s observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other “absurd” associations, that “it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected”. And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.’

In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr Watson, ‘when you have eliminated the impossible, whatever remains, however improbable, must be the truth.’

(7) *Coherence*: On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease – in the expression of the Advisory Committee to the Surgeon-General it should have coherence.

Thus in the discussion of lung cancer the Committee finds its association with cigarette smoking coherent with the temporal rise that has taken place in the two variables over the last generation and with the sex difference in mortality – features that might well apply in an occupational problem. The known urban/rural ratio of lung cancer mortality does not detract from coherence, nor the restriction of the effect to the lung.

Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man. Arsenic can undoubtedly cause cancer of the skin in man but it has never been possible to demonstrate such an effect on any other animal. In a wider field John Snow’s epidemiological observations on the conveyance of cholera by the water from the Broad Street pump would have been put almost beyond dispute if Robert Koch had been then around to isolate the vibrio from the baby’s nappies, the well itself and the gentleman in delicate health from Brighton. Yet the fact that Koch’s work was to be awaited another thirty years did not really weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day – both just and unjust.

(8) *Experiment*: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest

support for the causation hypothesis may be revealed.

(9) *Analogy*: In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Tests of Significance

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.

Nearly forty years ago, amongst the studies of occupational health that I made for the Industrial Health Research Board of the Medical Research Council was one that concerned the workers in the cotton-spinning mills of Lancashire (Hill 1930). The question that I had to answer, by the use of the National Health Insurance records of that time, was this: Do the workers in the cardroom of the spinning mill, who tend the machines that clean the raw cotton, have a sickness experience in any way different from that of other operatives in the same mills who are relatively unexposed to the dust and fibre that were features of the cardroom? The answer was an unqualified 'Yes'. From age 30 to age 60 the cardroom workers suffered over three times as much from respiratory causes of illness whereas from non-respiratory causes their experience was not different from that of the other workers. This pronounced difference with the respiratory causes was derived not from abnormally long periods of sickness but rather from an excessive number of repeated absences from work of the cardroom workers.

All this has rightly passed into the limbo of forgotten things. What interests me today is this: My results were set out for men and women separately and for half a dozen age groups in 36 tables. So there were plenty of sums. Yet I cannot find that anywhere I thought it necessary to use a test of significance. The evidence was so clear-cut, the differences between the groups were mainly so large, the contrast between respiratory and non-respiratory causes of illness so specific, that no formal tests could really contribute anything of value to the argument. So why use them?

Would we think or act that way today? I rather doubt it. Between the two world wars there was a strong case for emphasizing to the clinician and other research workers the importance of not overlooking the effects of the play of chance upon their data. Perhaps too often generalities were based upon two men and a laboratory dog while the treatment of choice was deduced from a difference between two bedfuls of patients and might easily have no true meaning. It was therefore a useful corrective for statisticians to stress, and to teach the need for, tests of significance merely to serve as guides to caution before drawing a conclusion, before inflating the particular to the general.

I wonder whether the pendulum has not swung too far – not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the USA where, I am told, some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary – because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the *t* table diverts attention from the inadequacies of the fare. Only a tithe, and an unknown tithe, of the factory personnel volunteer for some procedure or interview, 20% of patients treated in some particular way are lost to sight, 30% of a randomly-drawn sample are never contacted. The sample may, indeed, be akin to that of the man who, according to Swift, 'had a mind to sell his house and carried a piece of brick in his pocket, which he showed as a pattern to encourage purchasers'. The writer, the editor and the reader are unmoved. The magic formulæ are there.

Of course I exaggerate. Yet too often I suspect we waste a deal of time, we grasp the shadow and

lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P. And far too often we deduce 'no difference' from 'no significant difference'. Like fire, the χ^2 test is an excellent servant and a bad master.

The Case for Action

Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it – or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action. If this be operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

While that is a commendable ambition it almost inevitably leads us to introduce differential standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.

On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil

to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day.

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Exhibit 2

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

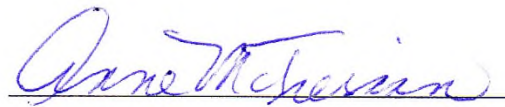
**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
ANNE MCTIERNAN, MD, PHD**

Date: November 16, 2018



Anne McTiernan, MD, PhD

Table of Contents

Mandate.....	3
Credentials, Expertise, and Experience.....	3
Overall Approach	7
Executive Summary.....	8
The Science of Epidemiology	10
Terminology in Epidemiological Studies	11
Types of Epidemiologic Studies on Ovarian Cancer and Exposure to Talcum Powder Products	18
Critical Components to Both Case-control and Cohort Studies.....	18
Case-control Studies	19
Cohort Studies.....	20
Meta-analyses.....	21
Possible Sources of Bias in Epidemiologic Studies Reviewed	22
Causal Inference in Epidemiology	25
Methods Used for this Review.....	30
Epidemiologic Evidence on the Association between Talcum Powder Products Use and Ovarian Cancer Risk	31
Case-control Studies	31
Prospective Cohort Studies.....	42
Meta-Analyses and Pooled Analyses	48
Asbestos, Fibrous Talc, and Heavy Metals in Talcum Powder Products.....	56
Biological Mechanisms.....	58
Evidence of Migration of Talcum Powder Products (Talc, Asbestos, Other Minerals) to the Ovary and Fallopian Tubes	58
Inflammation in the Causal Pathway between Talcum Powder Product Use and Ovarian Cancer Development.....	59
Additional Evidence of Biological Mechanisms	60
Summary of Findings: Weight of the Evidence/Bradford Hill Analysis	63
CONCLUSION.....	68
Tables: Epidemiological Studies of Talcum Powder Product Use and Risk of Ovarian Cancer.....	69
Table 1: Case-Control Studies	69
Table 2: Prospective Cohort Studies	73

Table 3: Meta-analyses	75
Table 4: Pooled Analysis	77
References	78
Additional Materials and Data Considered	84

Mandate

I have been retained to review the current state of the scientific literature regarding talcum powder products and opine on whether those products cause ovarian cancer. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within. All my opinions in this report are based upon a reasonable degree of scientific and medical certainty. My time is billed at \$450 per hour for the literature review and preparation of this report. I have not previously provided expert testimony in legal cases.

Credentials, Expertise, and Experience

I am a Full Member at the Fred Hutchinson Cancer Research Center in Seattle, Washington, Division of Public Health Sciences, Program in Epidemiology. I am also a Full Research Professor at the University of Washington School of Public Health, Department of Epidemiology, and the University of Washington School of Medicine, Department of Medicine, Division of Geriatrics. I am an elected member of the American College of Epidemiology, the Obesity Society, and the American College of Sports Medicine. From 2002-2012, I directed the Fred Hutchinson Cancer Research Center's Prevention Center.

I have received several prestigious awards for my research work including: the American College of Sports Medicine Wolffe Lecture, 2018, the American College of Sports Medicine Citation Award, 2012; the McDougall Mentoring Award, Fred Hutchinson Cancer Research Center, 2011; Komen for the Cure Scientific Advisory Council/Komen Scholars, 2010-2012; the University of Washington Roger E. Moe Award for Translational Research 2009; and the Joan P. Liman MD Award, Recipient, New York Medical College, 1989.

I received my PhD in Epidemiology in 1982 from the University of Washington, and my MD degree in 1989 from New York Medical College. I completed Internal Medicine residency training from the University of Washington in 1992. For the past 25 years, I have focused on epidemiologic research, primarily in cancer and women's health. My research studies used the methodology employed in the talcum powder products and ovarian cancer studies, namely, case-control studies, cohort studies, and meta-analyses. In addition, I have had leadership positions for several randomized controlled trials

testing interventions to prevent cancer. I have published over 400 scientific manuscripts in peer-reviewed medical and scientific journals, have contributed to several academic texts, and have edited two academic texts.

I have held several leadership positions in scientific U.S. Government work. Most recently, I was a member of the 2018 U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee and was a member of the 2008 U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee. I served as chair of the Cancer subcommittees for both Committees. I have served on, or chaired, grant review panels for the U.S. Department of Defense Congressionally Directed Medical Research Programs and the National Institutes of Health, and serve as a program reviewer for NCI intramural epidemiologic research branches and for NCI comprehensive cancer centers.

I have served on editorial boards for the American Association for Cancer Research Cancer Prevention Journal, the Journal of Women's Health, and Medscape Women's Health. I have reviewed manuscripts for over a dozen prestigious journals including: JAMA, Journal of the National Cancer Society, Archives of Internal Medicine, American Journal of Epidemiology, Annals of Internal Medicine, European Journal of Cancer, British Journal of Cancer, Cancer Causes & Control, Cancer Epidemiology Biomarkers & Prevention, Annals of Epidemiology, Epidemiology, and Nutrition.

My research funding has been provided by the U.S. National Cancer Institute, the National Institutes of Health, the National Heart Lung & Blood Institute, Komen for the Cure, the Breast Cancer Research Foundation, National Cancer Institute Canada, and various pharmaceutical companies and other foundations. I have been Principal Investigator of several randomized clinical trials testing effects of various agents in relation to prevention of breast and other cancers, including exemestane, raloxifene, tamoxifen, aspirin, and vitamin D. In addition, I have been Principal Investigator of four randomized clinical trials testing effects of weight loss and exercise on biomarkers of breast and other cancers. I am co-investigator of a pending National Cancer Institute funded trial testing the effect of exercise on quality of life in women with ovarian cancer. I was Principal Investigator of the Seattle site of a prospective cohort study of 1100 breast cancer survivors that investigated associations of hormones, inflammation, diet, exercise, obesity, and breast cancer survival. I was Principal Investigator of a case-control study of thyroid cancer and hormones in women, and co-investigator of a case-control study of

breast cancer in men. I have published on data from other case-control studies including studies on breast cancer, pituitary tumors, melanoma, and colorectal adenomas. I have collaborated in several prospective cohort studies, resulting in lead, senior, and co-authorship of several epidemiologic manuscripts. These included the Women's Health Initiative Observational Study, the Tromso study, the Carotene and Retinol Efficacy Trial cohort, the VITAL cohort, and the Pancreatic Cancer Cohort Consortium.

While my major focus is in epidemiology of breast cancer, I have also published on ovarian cancer, on gynecologic cancers in general, and on women's cancers, as described below, as well as on colorectal, pancreas, melanoma, and prostate cancers. In my randomized clinical trials and prospective cohort studies, I have investigated the effects of weight loss and exercise on biomarkers of inflammation, which is highly relevant to the topic of this report, because inflammation may be one mechanism linking talcum powder products exposure and risk of ovarian cancer.

My international work in epidemiology has included work with the International Association for Research in Cancer (IARC), the World Cancer Research Fund, and the Norwegian Tromso and EBBA studies. For IARC, I chaired a working group on mechanisms for a monograph on obesity, physical activity, and cancer risk (IARC Handbook of Cancer Prevention 2002: Physical Activity and Weight Control, 2000-1). For the World Cancer Research Fund, I am a member of the advisory panel of experts that guides interpretation of meta-analyses and systematic reviews of nutrition, physical activity, obesity, and risk for many cancers including ovarian cancer (<http://wcrf.org/sites/default/files/Ovarian-Cancer-2014-Report.pdf>).

From 1992 to 1997, I was the Project Director for clinical work at the Women's Health Initiative Clinical Coordinating Center. I held this role from the inception of the Women's Health Initiative, and therefore directed all aspects of development and implementation of the three clinical trials and observational study. This included development of questionnaires and protocols. Of interest to ovarian cancer and talcum powder products, one of the Women's Health Initiative questionnaires includes questions about use of talcum powder products. Furthermore, ovarian cancer was one of the primary cancers included as an outcome in this study. As Project Director, I oversaw development of the protocol and procedures for ascertainment and adjudication of cancer outcomes, including ovarian cancer. When I stepped down as Project Director (to lead my own National Cancer Institute funded studies), I retained leadership of

the outcomes work for the Women's Health Initiative through 2005. This outcomes work entailed identifying cases of specific diseases such as cancer (including ovarian), collecting medical records, and classifying cases according to standardized criteria.

Although I have not personally conducted research on talcum powder products use and risk for ovarian cancer, I have published several manuscripts on gynecologic cancers, including prevention of ovarian cancer in women at high genetic risk, as well as effects of weight and exercise on risk for ovarian cancer and on survivorship in ovarian cancer patients. In addition, I am co-investigator of a National Cancer Institute grant to test an exercise intervention on quality of life in women with ovarian cancer.

While my expertise is in the area of epidemiology, primarily in women's health and cancer research, I regularly consider the reports and studies from different scientific and medical fields including pathology, oncology, gynecology, physiology, molecular biology, and toxicology, and therefore, I have experience and expertise to consider evidence presented by experts in these fields, as I do when I prepare scientific manuscripts and grant proposals, when I review grants and manuscripts for government and private funding agencies, and when I do peer-reviewing for scientific and medical journals. Attached as Exhibit A to this report is a current copy of my curriculum vitae.

Overall Approach

The foundation for this report is based upon my education, expertise, and years of experience in designing, conducting, and interpreting epidemiologic studies, as well as my medical training. I drew upon my years of experience with synthesizing and interpreting large numbers of epidemiologic studies for comprehensive reports including work for the U.S. government, the World Health Organization International Agency for Research on Cancer (IARC), and the World Cancer Research Fund. My opinions are based on the published epidemiologic evidence including original case-control and cohort studies, systematic reviews, meta-analyses, and pooled analyses on the topic of talcum powder products exposure and risk of ovarian cancer. In reviewing the epidemiologic literature, I used my experience as a researcher in evaluating study quality, and in determining evidence of association between talcum powder products and ovarian cancer in terms of estimated size of the effect and statistical significance. I drew upon my 36 years as a PhD-trained epidemiologist and 26 years as an MD-trained clinical scientist.

In developing my opinions in this report, I applied the same rigor and standards as I utilize in my academic and research work. In addition to my review of epidemiologic studies, I also considered and reviewed clinical, pathological, and biologic and mechanistic evidence regarding talcum powder product exposure and ovarian cancer development.

Executive Summary

This review assessed relevant published epidemiologic evidence on the association between use of talcum powder products in the genital/perineal area and risk of developing epithelial ovarian cancer. My review, as discussed more fully in this report, included 38 publications in Medline referenced scientific journals. Of these papers, 28 presented data from case-control studies(1-28), 5 presented results from 3 cohort studies(29-33), 7 were meta-analyses of all epidemiologic studies up to a set date(11, 22, 34-38), and 1 was a pooled analysis of 8 case-control studies(39). All of these form the basis for the conclusions below. The meta-analyses, which included data summarized from all published case-control and cohort studies, consistently showed that ever use of talcum powder products in the genital/perineal area is associated with a statistically significant 22 - 31% increased risk of developing epithelial ovarian cancer overall compared with never-users. Further, the meta-analyses found a statistically significant 24 – 32% increased risk of developing serous ovarian cancer—the most common subtype of epithelial ovarian cancer—in women who had ever used talcum powder products compared with never-users. The pooled analysis, which included data from 5 previously published and 3 unpublished case-control studies, found similar statistically significant increased risks for overall epithelial ovarian cancer and serous ovarian cancer (24%). The two most recent meta-analyses, and the pooled analysis, found evidence of relationships between increasing amount of exposure to talcum powder products in the perineal/genital area (including frequency, years of use, and estimates of lifetime applications) and increased risk of developing epithelial ovarian cancer (i.e., dose-response relationships).

Published laboratory and clinical studies on talc exposure and ovarian carcinogenesis have shown that in humans, talc can migrate from the perineum to the ovaries and that it can cause an inflammatory response. Elevated levels of biomarkers of inflammation (such as cytokines), as well as oxidative stress, provide biologically plausible pathways by which talcum powder product exposure can induce neoplastic transformation and result in ovarian cancer.

Given the frequency with which asbestos, a known carcinogen has been found in cosmetic and personal-use talc products, I reviewed the literature on the epidemiology of asbestos and risk of ovarian cancer. Due to the presence of not only asbestos but fibrous talc, heavy metals, and fragrance, I also reviewed literature on the carcinogenic properties of these constituents. IARC noted in its 2012 report that a causal association between exposure to asbestos and cancer of the ovary was clearly established.(40,

41) IARC has classified asbestos and talc containing asbestiform fibers grown in an asbestiform habit as Class 1 carcinogens(40, 42). Talc fibers grown in an asbestiform habit are often referred to as “fibrous talc.” The elongated features of fibrous talc have many of the carcinogenic properties of asbestos that are known to cause an inflammatory process.(40) The additional chemicals present in talcum powder products discussed above were also classified by IARC to be carcinogenic(40), contributing to the biologically plausible mechanisms to explain the carcinogenic effects of talcum powder products.

The epidemiologic evidence in total, along with the biological and pathological evidence, fits virtually all of the Bradford Hill aspects of causation(43), namely: strength, consistency across populations, temporality, biologic gradient (dose-response), plausibility, coherence, and analogy. The weight of the evidence related to genital use of talcum powder products and ovarian cancer development demonstrates a consistent increased risk. There are many instances in which relative risks less than 1.5 are widely accepted within the scientific community as being causative and have strong public health and clinical ramifications, as I point out in the report. Given the high prevalence of use of talcum powder products (as much as half of women in some studies), a relative risk/odds ratio in the range observed in these studies can have profound effects on clinical events and public health.

In my opinion, as an epidemiologist and physician, stated to a reasonable degree of medical and scientific certainty, use of talcum powder products, including Johnson & Johnson Baby Powder and Shower to Shower, in the genital/perineal area can cause ovarian cancer. I base this opinion on the statistically significant elevated risk estimates (relative risk, odds ratios) seen when the epidemiologic data are combined, the pathological evidence, the consistency of results across geographic areas and in different race/ethnic groups, the evidence of a positive dose-response effect, and the plausible biological mechanisms.

The Science of Epidemiology

Epidemiology is the science of diseases in human populations. Epidemiologists study patterns of disease occurrence to determine causes of the disease of interest, with an aim of finding ways to prevent the disease from occurring. Epidemiological research describes and seeks to explain the distribution of health and disease within human populations. Its methods are based mainly on comparative observations made at the level of individuals within populations. This type of investigation is known as observational. By relating differences in circumstances and behavior to differences in the incidence of disease, associations are identified that may or may not be causal.

In epidemiological studies, an 'exposure' is a factor or condition that may or may not influence the risk of disease. For assessing effects of some exposures, epidemiologists may employ randomized controlled clinical trials, but for exposures that have possible adverse effects with little known benefit, such studies would be unethical. For example, the effects of vitamin supplements have been tested in large-scale clinical trials to determine effects on risk for several cancers. This was considered ethical because the expectation was that the vitamin supplements could have benefit, and were unlikely to have risk, for study participants. For toxicological exposures, however, with little expectation of benefit to offset possible adverse effects, observational studies will usually be the only available epidemiological evidence.

Much public health knowledge derives from epidemiological studies. For example, observational epidemiological studies show us that individuals who drink excessive amounts of alcohol have a high risk for developing liver failure and other diseases. Such studies have shown that persons with obesity have a high risk for developing diabetes and that smokers have high risk for developing lung cancer. Similarly, the effects of toxic agents on risk for several diseases have been identified through observational epidemiological studies. Examples include the effect of lead paint on cognitive development in children; the effect of radium exposure on bone health, blood abnormalities, and cancers; and the effect of second hand smoke on risk for lung cancer in nonsmokers.

The associations between talcum powder product use and risk for ovarian cancer have been studied only in two types of epidemiologic studies—case-control and cohort—and therefore this description of epidemiologic methodology below is limited to those types of studies.

Terminology in Epidemiological Studies

Disease incidence: The incidence of a disease is the number of new cases that occur. An incidence rate is the number of new cases that occur per number of persons over an interval of time. Typically, for cancer, incidence rates per 100,000 individuals per year are determined. The incidence rate for ovarian cancer in the U.S. is approximately 11.7/100,000 women/year (<https://seer.cancer.gov/statfacts/html/ovary.html>).

Risk: The risk of a disease refers to likelihood of its occurrence. In epidemiological studies, risk is usually used in relative terms, that is, the risk of developing cancer in one group versus the risk in another group. In cancer epidemiology, the risk almost exclusively refers to risk of incident cancer, that is, risk of a new cancer occurrence.

Risk factor: The World Health Organization defines a risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (http://www.who.int/topics/risk_factors/en/). Risk factors can be inherent, such as sex, age, and genetics; lifestyle-related such as diet, physical activity, or smoking; health related such as menstrual factors, reproductive history, or history of infectious diseases; toxic exposures such as minerals, metals, chemicals, or radiation; or medical, such as use of particular medications.

Exposures: In epidemiological studies, an ‘exposure’ is a factor or condition that may increase or decrease the risk of disease. In this report, use of talcum powder products is the ‘exposure’ investigated. Self-reporting of exposure could result in incomplete information. Some women may over-report use of personal products, while others may not recall whether they used the products, how often or at what quantity they used them, or for how long they continued using them. Studies in which participants are queried by trained interviewers may be able to obtain information in greater detail than when participants complete questions on a form.⁽⁴⁴⁾ However, women may be reluctant to relay sensitive personal information to an interviewer as opposed to a self-administered form.⁽⁴⁴⁾ This type of

systematic bias, however, would underestimate the relative risk, suggesting that effects of talcum powder product use in the perineal area may be stronger than reported in epidemiologic studies.

Association: Epidemiologists use the term association to describe how a disease occurrence varies as a result of the effect of an exposure. A positive association indicates that the exposure increases risk of the outcome; a negative association indicates that the exposure decreases risk of the outcome.

Etiology: The etiology is the cause or origin of a disease or condition.

Multi-factorial etiology: Very few cancers occur as a result of only one cause. Most, on the other hand, have several likely causes, each with different levels of effect. The most common risk factor for cancer is age, as older persons have increased risk for developing most of the common cancers. So, even though certain human papilloma viruses increase risk for head and neck cancers, their effect is most often seen with increasing age despite individuals acquiring the virus at a young age. For some cancers, exposures add to the effects of other exposures, or even multiply their effects. For example, both smoking and alcohol use increase risk for squamous cell carcinoma of the esophagus, but individuals who both smoke and drink have a risk of this cancer that is greater than what would be expected by adding the effects of the two exposures.

Latency period: The length of time between when a person is exposed to a causal agent and when their cancer is first diagnosed is called the latent period. This period is typically years to decades. For exposures that continue over time, it may not be possible to determine the latency period of that cancer.

Relative risk, odds ratio, and hazard ratio: The strength of a relationship between an exposure and the occurrence of disease is commonly expressed in terms of relative risk. In cohort studies, relative risk is the ratio of risk (or incidence) of a disease among people with an exposure to that among people without that exposure. In cohort studies, the hazard ratio can be used, and is the chance of an event occurring in one group (exposed) divided by the chance of the event occurring in another group (non-exposed). In case-control studies, the odds ratio is used, which is the ratio of the odds of exposure among cases to the odds of exposure among controls. Relative risks, odds ratios, and hazard ratios

above 1.0 indicate an increased risk, while those below 1.0 imply a protective effect. Therefore, a relative risk of 1.3 represents a 30% increased risk.

Statistical analyses: Epidemiologists use several types of statistical analyses to determine the size and significance of relationships among variables in sets of data. The most common in observational studies are the relative risk, odds ratio, and hazard ratio. These estimates are based on individual studies, or on meta-analyses, which are based on data from multiple studies. To determine the likelihood of these being true estimates of risk, rather than just occurring by chance, epidemiologists determine the statistical significance. For the relative risk, odds ratio, and hazard ratio, we calculate a confidence interval (CI), which shows the range of values that the true risk estimate likely represents. Most commonly, we use 95% CI, which means we are 95% sure that a true relative risk or odds ratio lies within that interval of numbers. If a confidence interval includes the number 1.0, then we say the association between the exposure and the disease could be null. Some epidemiologists consider a CI that has 1.0 at one end of the range to be of “marginal statistical significance.” A similar statistic is the p-value, which estimates how likely the observed association is likely due to chance. Epidemiologists often consider a p-value less than or equal to 0.05 as “statistically significant,” and often describe p-values between 0.05 and 0.09 as “marginally statistically significant.” However, the term just refers to the likelihood of a chance finding.

Both confidence intervals and p-values depend largely on the size of the population studied. If a relative risk/odds ratio indicates an effect that is consistent across studies, or that is large, we are less likely to reject the likelihood of true association, even if the confidence interval includes 1.0 or if the p-value is greater than 0.05.

Sample size: Because development of cancer can be a random event, epidemiologists strive to determine whether an association between an exposure and disease could have occurred by chance. If the study is designed appropriately, the chance of random-ness explaining observed associations is lessened. The number of cases of cancer within the study is a critical element to determining likelihood of causality.

Standardized incidence ratio and standardized mortality ratio: In some epidemiologic studies, only highly exposed persons are available for study. This is a common occurrence in studies of occupations with high levels of exposures to carcinogens, such as asbestos. Researchers typically then compare the incidence (or mortality) in the exposed cohort with the general population from which the exposed cohort is drawn. The standardized incidence ratio compares the actual versus expected number of cases of a disease, using the population data to determine expected numbers. Similarly, the standardized mortality ratio compares actual versus expected numbers of cause-specific or overall deaths. The standardized incidence ratio and standardized mortality ratio are similar to relative risks, and 95% confidence intervals are often presented.

Dose-response: “Dose response” began as a medical concept where it denotes a change in the effect of a medication or treatment according to the dose used. This concept can be applied to any exposure, including potentially toxic agents such as talcum powder products. The demonstration of a biological gradient adds weight to evidence that an exposure may be causal.

Dose response effects may be linear, where an increase in the exposure increases risk of disease at each level of increase in the exposure. A common example is the relationship between average packs/day and years of cigarette smoking and risk for lung cancer. Alternatively, there may be a ‘threshold’ below which there is no effect seen, but above which there is an effect. An example is the association between exposure to menopausal hormone therapy; use for short periods has little effect on risk of breast cancer, but risk consistently increases for five years’ or longer use.

Alternatively, the effect may be to influence risk one way at both low and high levels of exposure, but the other way at intermediate levels of exposure, shown as ‘J’- or ‘U’-shaped curves. In such cases, the exposure is evidently beneficial or harmful only within certain ranges. For example, intake of alcohol at small amounts has been related in some studies to lower risk of cardiovascular disease, whereas heavy intake increases risk.

Some exposures that are continuous variables are often reported in discrete categories. Although this is done for statistical reasons and can make effects easier to detect, the number and location of category boundaries may obscure the true relationship between exposure and the outcome, and non-linear effects of exposure may be missed if inappropriate categories are used.

Bias: A systematic error in the design, recruitment, data collection or analysis that results in a mistaken estimation of the true effect of the exposure and the outcome.

Confounding: This type of bias occurs when a third variable interferes with a true relationship between an exposure and an outcome. A confounding variable is one that is related to the risk of disease and to the exposure. It is not by itself a cause of the disease and does not lie in the pathway between the exposure and disease. A classic example is that individuals who report carrying matches in their pockets are more likely to develop lung cancer than individuals who do not carry matches. However, the true relationship is between smoking and lung cancer. Smokers are more likely to carry matches, and it is the smoking that is the true cause. The epidemiologic studies reviewed for this report all adjusted for potential confounding factors.

Effect modification: In some persons, an exposure increases risk of disease while in others it has no effect or has a smaller effect. This is called effect modification. An example is that obesity has a larger effect on risk for colon cancer in men than in women.

Generalizability: The goal for epidemiologic research is to identify causes of disease that can be applicable to all populations. Most modern-day case-control studies attempt to do this by conducting population-based studies. That is, they identify all cases of a cancer occurring in a population and attempt to interview as many of those cases as possible. They also identify a similar sample of persons from the same population who do not have cancer and attempt to interview as many of those as possible. Many of the case-control studies of talcum powder products identified cases through population-based cancer registries, which register almost 100% of cases of cancer occurring in the population served by the registry. These population-based studies are better able to produce results that are generalizable to the whole population. Hospital-based case-control studies of ovarian cancer include all cases of the cancer that present to a hospital and compare them to a comparable group of hospitalized patients without cancer. While the comparisons between cases and controls can be valid, the generalizability of the results to the population can be low if patients from the recruiting hospital differ from the population as a whole.

Generalizability can be more of an issue for cohort studies, depending on how the study participants were recruited. Three cohort studies have reported on talcum powder product use and ovarian cancer risk. The Women's Health Initiative recruited from the general population of postmenopausal women from 40 clinical centers around the U.S. The rate of response was only around 1-2%, however, and therefore the cohort is unlikely to represent the population of American postmenopausal women. The Nurses' Health Study recruited nurses from around the U.S. Their rate of response was higher than for the Women's Health Initiative, but they are all nurses, and therefore have different health knowledge, income, and socioeconomic status compared with the general U.S. population. The Sisters' Study recruited from the general population, targeting women who had at least one sister with breast cancer. The responding participants therefore represent only women with a family history of breast cancer, and given their self-selection, likely differ from the general population in vulnerability to cancer and other characteristics.

Exposure measurement: Defining whether a person is exposed to a potentially causal agent is critical to the science of epidemiology. For many exposures, we must rely on what the individual can tell us about their health habits, lifestyle, work history, and use of products and medications. Recall of these variables can be challenging. Epidemiologists, therefore, often have interviewers use tools to jog participants' memories, such as anchoring around particular ages and life events. The most thorough case-control studies queried about both frequency and duration of use of talcum powder products, as well as brand and type of product, and areas of exposure (e.g., perineal, sanitary napkin, other body areas, diaphragm, etc.) The ascertainment of use of talcum powder products is difficult, especially in determining dose of exposure, because women may have been using powders without being aware of what the product contained. Furthermore, information on the variable contents of talcum powder products (talc, fibrous talc, asbestos, other metals, fragrance) was not available to the scientists conducting the epidemiologic studies. While many epidemiologic case-control studies of talcum powder products and ovarian cancer risk asked women for brand names and dates of use, and analyzed data separately by likely powder contents, these analyses will not have been able to identify the various constituents of talcum powder products.

The Women's Health Initiative asked about duration of use of talcum powder products but did not ask about frequency of use.⁽²⁹⁾ The Nurses' Health Study asked about frequency of use but did not query regarding duration of use.⁽³¹⁾ The Sisters' Study asked participants about use of talcum powder

products in the 12 months before study enrollment, and the frequency of use.(30) None of the cohorts, therefore was able to estimate total lifetime dose of talcum powder product exposure. As described below, under-reporting of exposures will underestimate a true relative risk.(45) Therefore, the estimated relative risks in studies that looked at effects of talcum powder product use and risk of ovarian cancer may be under-estimates.

Diagnosis and classification of disease outcome: “Outcome” refer to the disease or health condition of interest; in this report, any type of epithelial ovarian cancer is the outcome. In some reports, cancers of the fallopian tubes and peritoneum are combined with epithelial ovarian cancer, as they are believed to be the same biological process and are treated the same as ovarian cancer with surgery and chemotherapy (<https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq>).

Determination of outcomes (sometimes called “events”) is a critical part of epidemiologic research. If cases of a disease are over- or under-counted, results of exposure-disease associations will be skewed. If the source of cases differs from the source of controls, comparisons between cases and controls may be biased. In case-control studies, researchers try to include all cases that were newly diagnosed with the disease in a defined population within a set period. Population-based cancer studies often identify cases through population-based cancer registries. Hospital-based studies, conversely, identify cases that were newly diagnosed in one or more hospitals. Whichever method is used, researchers try to include and interview as high a proportion as possible of identified cases, to reduce chances of biased results.

For epidemiologic studies of cancer, it is important to identify, at the minimum, the type of cancer, stage of cancer at diagnosis, and subtype of cancer. Using pathologists’ reports from medical records, trained coders classify patients into the correct categories depending on the pathology and other medical records. There are several different subtypes of cancer of the ovary. Over 90% originate in epithelial tissues and are called “epithelial ovarian cancers.” The remaining 10% originate in other ovarian tissues (germ cell or sex-cord stromal). Of the epithelial ovarian cancers, approximately 70% are serous, 10% are endometrioid, 12% are clear cell, 3% are mucinous, 1% are Malignant Brenner, and the remaining are mixed histologies.(46) Epithelial ovarian cancer may be invasive or borderline. Only epithelial ovarian cancer has been studied in relation to use of talcum powder products. Therefore, in this report, “ovarian cancer” refers to “epithelial ovarian cancer.”

Types of Epidemiologic Studies on Ovarian Cancer and Exposure to Talcum Powder Products

Epidemiologists have assessed the relationships between use of talcum powder products and risk of ovarian cancer development, using several types of epidemiologic studies. The studies with the greatest number of cases of ovarian cancer used case-control designs. Most of these were designed specifically to address use of talcum powder products as a potential cause of ovarian cancer. Three cohort studies have also reported on associations between talcum powder product use and risk of ovarian cancer. These cohort studies were designed to test hypotheses relating hundreds of exposures to scores of disease outcomes including common cancers, cardiovascular disease, cerebrovascular disease, musculoskeletal diseases, and others. Finally, after several epidemiologic studies were published, researchers combined data from these studies using either meta-analyses or a pooled analysis. The pooled analysis also included data from previously unpublished studies, and therefore provide additional information beyond just summarizing results of published studies. All of these studies contribute to the science of the epidemiologic evidence relating use of talcum powder products to risk of ovarian cancer development. The totality of evidence on the causal effect of talcum powder product use on ovarian cancer development relies on data from epidemiologic studies, pathological evidence of migration to the ovaries of talc and other contents of talcum powder products (such as asbestos), and laboratory evidence.

Critical Components to Both Case-control and Cohort Studies

- 1) The accurate and complete ascertainment of cases. In case-control studies, this means that all cases of ovarian cancer should be identified in a given population and as high percent of them should be included in the study as possible. The controls should be free of ovarian cancer and should be as similar as possible to the cases except for the exposure under study. In cohort studies, this means that all individuals should be followed over time to determine how many did or did not develop ovarian cancer. For both types of studies, cases should be confirmed by medical record and pathological report review.
- 2) Precise determination of exposure. In both case-control and cohort studies, both cases and non-cases should have completed questionnaires about their current and past history of use of talcum powder products, including how often they used the products, when they began use, and number of years used.

In case-control studies, this is often done with the help of a trained interviewer. In cohort studies, which typically involve larger numbers of participants because only a small fraction will go on to develop specific diseases, questionnaires are usually self-administered without the assistance of an interviewer. In cohort studies, exposures should be updated after the baseline assessments, to ensure that changes in exposure can be captured. For an exposure like talcum powder product use, lifetime use would be relevant for determining total exposure. For both case-control and cohort studies, determining early life exposures depend on participants' ability to recall typical use patterns. Interviewer-administered surveys would typically include prompts to help participants recall past habits. Self-administered questionnaires may include some printed prompts, but these are usually minimal.

For a rare endpoint like ovarian cancer, a cohort must be followed for decades in order for a sufficient number of cases to accrue to determine effects of particular exposures. Therefore, there is the possibility of bias towards the null via changes in behavior over the course of the decades of follow-up. A woman who was originally classified as an "ever" talc user will remain an "ever" user even if she subsequently discontinued talc use. A "never" user who subsequently begins talc use will always be misclassified as a never user unless a follow-up survey records her change in status.

In ideal situations, the precise nature of the exposure would be verified. Despite habitual use, however, quantification of exposure is difficult.

(3) For both case-control and cohort studies, the populations should be well-characterized, so that any potential confounding variables can be accounted for in comparing exposure rates of cases and non-cases.

Case-control Studies

In case-control studies, individuals diagnosed with a specific type of cancer (cases) are compared with otherwise similar individuals who have not been diagnosed with cancer (controls). The control group is a sample of the population from which the cases arose and provides an estimate of how the exposures being studied are distributed in that population. In the ideal case, the controls will be similar to the cases on all variables other than the exposure under question. Therefore, epidemiologists often match

controls to cases on such variables as age, race, and ethnicity, or they include a large enough sample of participants that they can adjust for these variables.

Case-control studies can enroll a large number of cases, are usually less expensive than cohort studies, and can be completed over shorter periods of time. Relevant to this report, case-control studies also can be designed to answer specific questions related to one outcome, and participants can be queried in detail about certain exposures. Selection bias is an increasing problem if participation rates among case and control groups is substantially less than 100 percent, and where participation may be related (in different ways) to various exposures.

Case-control studies are subject to their own limitations, including recall bias, which can occur when participants' reports of various exposures are differentially affected by whether they are cases or controls in the study. This is a theoretical bias however; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls.⁽⁴⁷⁾

One of the case-control studies of talcum powder product use and ovarian cancer risk (1) addressed this issue by counting as "users" only women who had used talcum powder products for at least six months, on at least a monthly basis. This procedure minimizes the potential over-reporting of minimal exposure by cases versus controls.

For this report, I reviewed 28 case-control studies, for most of which the association between use of talcum powder products and risk of ovarian cancer was a primary research questions.

Cohort Studies

In prospective cohort studies (usually called cohort studies), the exposures of a large group (cohort) of people who are assumed to be healthy are assessed, and the group is followed over a period of time. During the follow-up period, some members of the cohort will be diagnosed with cancer, while others will not, and comparisons are then made between these two groups. Cohort studies may need to be very large (up to hundreds of thousands of participants) to have sufficient statistical power to identify factors that may increase cancer risk by on the order of 20 or 30 percent. In addition, meaningful

comparisons between cases and non-cases can be made only for factors that vary sufficiently within the cohort. Importantly, cohort studies must identify exposures of interest when participants are enrolled into the study, in order to determine effect of the exposures on eventual development of the outcome of interest. Alternatively, if an exposure is ascertained some time after enrollment (as in the Nurses' Health Study ascertainment of talcum powder product use), the researchers will consider the date of collection of that exposure data to be the start date for follow-up of study participants. Because cohort studies typically are designed to look at multiple outcomes such as cancers, cardiovascular diseases, mortality, and other diseases, information collected on exposures tends to be minimal, to pertain to current levels of exposure, and may not be updated during follow-up.

Cohort studies provide the opportunity to obtain repeated assessments of participants' exposures at regular intervals, which may improve the assessment of the exposures. However, for this to happen, the investigators need to have planned for repeated measures of the exposure. In published cohort studies of talcum powder products and ovarian cancer risk, no repeated measures of talcum powder products were reported.

In cohort studies, the ascertainment and adjudication of cancer outcomes can be accomplished by directly asking participants about illnesses and hospitalizations, and requesting medical records for reviewing these events. In some cases, ascertainment of disease events may be accomplished by linking to a cancer registry.

For this report, I reviewed results of 3 cohort studies, published in 5 papers. None were designed specifically to look at the association between talcum powder product use and risk of ovarian cancer. Further, none of these studies fully ascertained exposure to talc, as will be discussed below.

Meta-analyses

Because there can be random variations within individual epidemiologic studies, and because very large sample sizes may be needed to see effects on rare diseases, epidemiologists rarely make causal inferences based on results of one study. Rather, we look at the totality of epidemiologic studies to determine patterns of exposure-disease relationships. Meta-analysis is a method used to combine the statistical results of several studies to produce an average estimate of effect of an exposure on an

outcome of interest. These summary estimates can provide evidence regarding the presence or absence of an association and can allow examination of dose-response relationships. In the area of talcum powder products use and ovarian cancer, 7 meta-analyses have been published (11, 22, 34-38), two of which are very recent and covered all studies contained in the previous meta-analyses.(34, 35) Of the 7 meta-analyses, 2 were included within reports of individual case-control studies (11, 22); the two recent meta-analyses contained all studies included in these 2 meta-analyses as well.

Pooled analysis is a type of meta-analysis where original individual-level data from various published and/or unpublished epidemiological studies are combined and re-analyzed. The combination of data from multiple studies creates a larger data set and increased statistical power. One such pooled analysis was published on the relationship between talcum powder product use and risk of ovarian cancer, and is heavily cited in this report because of its significance in including very high numbers of women with ovarian cancer and controls, thereby providing a high degree of statistical power.(39)

The 7 meta-analyses that I reviewed for this report included data from available cohort and case-control studies. I also reviewed the pooled analysis of 8 case-control studies.(39) In addition to effect measures (relative risks, odds ratios, hazard ratios) and their confidence intervals (or other test of statistical significance such as p-value), I reviewed the number of people with and without disease for each exposure category, method of exposure ascertainment, estimated exposure categories, assessment of dose-response effects, and effect sizes for all epithelial ovarian cancer and for subtypes of epithelial ovarian cancer (invasive, borderline, serous, endometrioid, mucinous, clear cell).

Possible Sources of Bias in Epidemiologic Studies Reviewed

All studies of all types must be critically evaluated for both strengths and potential limitations in order to determine the totality of evidence. Limitations in epidemiologic studies are often characterized as biases. These include the biases listed below. It is important to note that the presence of bias does not render an epidemiologic study invalid. Rather, biases are issues that should be carefully considered when assessing how much weight should be given to individual studies, and what conclusions can be drawn from them.

Missing data: Both case-control and cohort studies can suffer from missing data. If the missing data items are related to the use of talcum powder products, then the estimated relative risks/odds ratios will likely be artificially low. If, in cohort studies, the cases of ovarian cancer are not identified, i.e., the cancer data are missing, the statistical power to detect statistically significant effects will be lessened. Both of these conditions would likely mean the true association between use of talcum powder products and risk of ovarian cancer is actually higher than what is observed in the epidemiologic studies.

Poor precision of exposure measurement: Determining whether, how much, and for how long women were exposed to talcum powder products is difficult. Women may not remember the brand of powder products they used, and contents of personal powder products may not be clear or may change over time. Women may not remember the amount of products used, frequency of use, and years of use.

Publication bias: The publication of epidemiologic studies depends on several factors. The investigators must have developed hypotheses about certain questions and designed the study accordingly, including asking the correct questions about the exposure and potential confounding variables, and collecting information from a sufficient number of participants. The investigators then need to perform statistical analyses, develop scientific manuscripts, and submit for journal publication. It may be difficult to find a journal that will accept null results (i.e. where an exposure is shown to not be related to an outcome).(48, 49) The pooled analysis of case-control studies provides some reassurance that publication bias is less likely for this association.(39) Of the 8 studies included in that analysis, 3 had not been previously published. Ever use of talcum powder products in the genital area produced odds ratios of 1.37 (95% CI 1.07–1.67), 1.36 (95% CI (1.06–1.74), and 0.99 (95% CI 0.70–1.41) for the 3 individual studies. That the confidence intervals overlapped, and that 2 of the 3 studies showed statistically significant associations, suggest low publication bias for the association between use of talcum powder products in the genital area and risk of developing ovarian cancer.

Cancer process affecting likelihood of exposure: If women used talcum powder products in the perineal area due to symptoms from an early cancer process, results of studies could be biased. Cohort studies often guard against this by eliminating cases that develop within a short time of study enrollment. Case-control studies guard against this by asking participants to recall exposures one or more years prior to their cancer diagnosis (and similarly ask controls to recall exposures at least one year prior to interview).

Confounding: Variables related to both use of talcum powder products and risk of ovarian cancer could mask the true relationship between these variables. Epidemiologists handle this by adjusting in the analysis for these potential confounding variables. All of the studies reviewed performed adjustment for several potential confounding variables. Those studies that presented both adjusted and unadjusted odds ratios/relative risks found little effect of confounding variables on these relationships.

Recall bias: For the case-control studies, media reports of associations between talc and ovarian cancer could have influenced cases such that they recalled use of talcum powder products to a greater degree than controls. However, the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward. Thus, “recall bias” is unlikely to be an issue. As mentioned above, recall bias is a theoretical bias; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls.(47)

Non-response bias: Case-control studies with low levels of response in cases or controls can be biased, in that the non-responding cases and controls could differ with respect to use of talcum powder products.

Differential results of cohort versus case-control studies: Ideally, results of case-control and cohort studies would be similar for the relationship between an exposure and risk of disease. However, there could be several reasons for discrepancy in results between case-control and cohort studies. The exposure measurement may differ in the two types of studies. For example, cohort studies may measure exposure at study entry without updating and without ascertaining lifetime exposure. The study would then have only one time point of an exposure that could significantly attenuate the observed associations between exposure and disease.

Population-based case-control versus hospital-based case-control studies: For some exposure-disease relationships, population-based case control studies are the most valid method of comparing risk for exposed versus non-exposed persons because the risks to public health can better be estimated. For others, however, hospital-based case control studies may provide important information because controls with illnesses may be more likely to recall exposures compared with healthy controls from the community, and therefore recall bias can be reduced.

Causal Inference in Epidemiology

The overarching goal of epidemiologic research is to determine likely causes of disease, in order to determine who is at risk for that disease and how to prevent the disease in individuals and populations. Much of epidemiologic observational research in cancer focuses on determining the *associations* between an exposure and an outcome. In other words, in a sample of individuals, are the number of persons exposed to an agent more likely to develop a cancer than those who are not exposed? There are several related questions. For example, will the persons who are exposed to a higher dose have an even greater risk than persons with little exposure? Will those exposed for a longer period of time have greater risk than those exposed for only a short time? Epidemiologists follow guidelines and logic in determining likelihood of an exposure causing cancer.(50) In addition to epidemiologic data, epidemiologists also consider plausible biological mechanisms to explain observed associations. The weight of evidence depends on the validity of the data as well as the clinical and biological evidence, if available, to explain these associations.

In epidemiology, and therefore in this report, a positive association means that the exposure in question increases risk for a disease or outcome. A negative association refers to an exposure decreasing risk for the outcome.

In 1965, English epidemiologist Sir Austin Bradford Hill attempted to describe several aspects of the causal relationship in a speech to the Royal Society of Medicine's newly-established Section of Occupational Medicine.(43) As Bradford Hill explained, this is not a checklist of factors to be counted: "What I do not believe—and this has been suggested—is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*."

These aspects of a causal relationship are:

Strength of the association. If the risk of developing cancer is several times higher in persons exposed to a toxic agent, that increases the likelihood of causality. It is not a necessary condition for establishing causality and providing recommendations for avoiding a potential cancer-causing agent, however.

Indeed, several carcinogens raise risk of cancer less than doubling of risk, but because of a high prevalence of exposure, can have major public health effects. Other exposures may be highly prevalent to certain groups such as factory workers; such exposures need to be minimized to meet government regulations for worker safety. Several examples follow:

Alcohol and risk for postmenopausal breast cancer: Risk for postmenopausal breast cancer increases by approximately 10% (a relative risk of 1.1) for each 10 gram/day intake of alcohol (the amount in a four-ounce glass of wine).(51) Women are advised to avoid alcohol or minimize alcohol intake to no more than one alcoholic drink per day to reduce risk for this cancer.(51) As Bradford Hill pointed out in his address: "We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so."(43)

Air pollution and risk for cardiovascular disease: A 2013 meta-analysis found that for each 10 $\mu\text{g}/\text{m}^3$ rise in $\text{PM}_{2.5}$, the air pollution caused by motor vehicles, yields an 15% increase in risk of cardiovascular disease (similar to a relative risk of 1.15). Given the widespread prevalence of exposure to ambient pollution, even modest contributions to cardiovascular disease risk can have a substantial effect on population health. (52)

Outdoor particulate matter air pollution and lung cancer: A 2014 meta-analysis including 18 studies showed a relative risk of 1.09 (95% CI 1.04-1.14) per 10- $\mu\text{g}/\text{m}^3$ of exposure to particulate matter ($\text{PM}_{2.5}$).(53) This is highly significant, because 10- $\mu\text{g}/\text{m}^3$ of exposure to $\text{PM}_{2.5}$ is the lowest recommended limit set by IARC for minimizing health effects of air pollution.

Benzene at work and risk of leukemia: In 2010, a meta-analysis of 15 epidemiologic studies found that worksite benzene exposure increased risk of any leukemia by 40% (relative risk 1.40, 95% CI 1.23-1.57).(54)

Estrogen-progestin menopausal hormone therapy and breast cancer risk: The Women's Health Initiative clinical trial showed that this type of hormone therapy increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk

for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke).(55) A meta-analysis of clinical trials and observational studies in 2018 found that use of this therapy increased risk of breast cancer by 59% (relative risk 1.59, 95% CI 1.40-1.81).(56) These results led to FDA-required label warnings on estrogen and progesterone therapy preparations(57), and to clinical warnings against use of estrogen plus progesterone for prevention of chronic conditions.(58)

Trichloroethylene and risk of kidney cancer: In 2012, a meta-analysis was published showing that occupational exposure to trichloroethylene was associated with an approximately 30% increased risk for kidney cancer (relative risk 1.32, 95% CI 1.17-1.50).(59)

Regular physical activity is associated with reduced risk for cardiovascular disease, diabetes, and various cancers in persons who meet national physical activity guidelines of 150 minutes/week of moderate-intensity aerobic activity.(60) In one large pooled analysis of 6 cohorts with 661,137 men and women, investigators found a 20% lower mortality risk among those performing less than the recommended minimum of 7.5 metabolic-equivalent hours per week (hazard ratio, 0.80 [95% CI, 0.78-0.82]), a 31% lower risk at 1 to 2 times the recommended minimum (hazard ratio, 0.69 [95% CI, 0.67-0.70]), and a 37% lower risk at 2 to 3 times the minimum (hazard ratio, 0.63 [95% CI, 0.62-0.65]).(61) To compare with the relative risks for adverse exposure, one would look at the inverse of the hazard ratios, i.e., 1.25, 1.45, and 1.59.

Intermittent intense sun exposure and risk of melanoma: A 2005 meta-analysis included data from 57 epidemiologic studies with 38,671 cases of melanoma, and found a relative risk of 1.61 (95% CI 1.31-1.99) for intermittent intense sun exposure.(62)

Prevention of skin cancer with use of sunscreen has also been observed, with similar effect sizes. In a 4.5-year trial with an additional 8-years follow-up, individuals randomly assigned to daily sunscreen use had almost a 40% reduced risk of squamous cell carcinoma (rate ratio, 0.62; 95% confidence interval, 0.38-0.99).(63) To compare with the relative risks for adverse exposure, one would look at the inverse of the risk ratio, i.e., 1.6.

Consistency of the association. A consistent association would be observed in various populations, places, circumstances, and times. Has the association been found in different countries, in persons from

various race/ethnic groups, and of different ages? This is also not a requirement, as there could be occasions when an exposure only increases risk for specific categories of individuals. An example, again from the breast cancer field, is that obesity increases risk for breast cancer occurring after menopause but decreases it for women who have not yet undergone menopause. Relevant to the association between ovarian cancer risk and use of talcum powder products, the association has been observed in the U.S., Canada, China, Australia, Israel, and the UK. While most data have been collected in Whites, a positive association between use of talcum powder products and risk for ovarian cancer has also been found in Blacks and Asians.

Specificity of the association: This suggests that if an exposure causes only one type of disease, that its causal link to that disease is strengthened. However, Bradford Hill recognized the limits of this aspect. One noxious agent, such as tobacco smoke, is an accepted cause of multiple cancers as well as cardiovascular disease. Similarly, one disease can have multiple causes. For example, lung cancer risk is increased with exposure to radon and asbestos, even in persons who do not smoke. In support of this, Bradford Hill stated, “One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation...”(43)

Temporality: The time course between exposure and disease occurrence is an important consideration. Bradford Hill was referring to the need to document that the exposure came before the disease, rather than something about the disease causing a person to come into contact with the exposure. This is why, for case-control studies, researchers have often queried women about their lifetime history of use of talcum powder products, beginning from young ages. Some cohort studies, on the other hand, asked about current use of these products when the women were first enrolled in the cohort. However, for all of these studies, only talcum powder product use prior to the cases’ diagnoses (and prior to a comparable time point for controls, in case-control studies) was counted as “exposure.”

Biologic gradient: This refers to the dose-response curve or the shape of the association between exposure and risk as the amount of exposure changes. If risk for a disease increases with increasing amount of exposure, the likelihood of a causal relationship is often increased. The exposure can be classified by total duration of exposure, by usual amount of exposure, or by a combination of these two. For use of talcum powder products, dose has been estimated by total years of use, by frequency of use, and by a combination of these two variables. It should be noted that ovarian talc particle burden may

not be influenced by number of applications of perineal talc usage(64), and therefore the typical dose-response relationship may not be necessary for establishing causality between perineal talcum powder product use and risk for ovarian cancer. Indeed, there are numerous substances for which there is no safe dose.

Plausibility: The association is strengthened if it is biologically plausible. However, Bradford Hill recognized that “What is biologically plausible depends upon the biological knowledge of the day.” It is important to note that biologic plausibility does not require proof of mechanism.

Coherence: The cause-and-effect interpretation of the data should not significantly conflict with the known facts about the natural history and biology of the disease. Therefore, for example, the concurrent rise in tobacco smoking rates and rise in lung cancer incidence in the 20th century in the U.S., as well as the more recent concurrent decrease in smoking rates and decrease in lung cancer occurrence, strengthen the association between smoking and lung cancer as causal. For the case of use of talcum powder products and ovarian cancer risk, the prevalence of other risk and protective factors (e.g., use of oral contraceptives, hysterectomy, and tubal ligation as protective factors, obesity as risk factor) changed over time in the general population. Therefore, it would be difficult to determine if ovarian cancer incidence time trends vary by changes in use of talcum powder products. The biology involves, as described below, the migration of talc to the ovaries, the inflammatory process which talc elicits, and the carcinogenetic effects of inflammation.

Experiment: The evidence from randomized controlled trials can provide strong support to observational evidence. However, in many situations, randomized controlled trials are not feasible. In the case of talcum powder products and ovarian cancer risk, a trial would have to be very large, involving 50,000 women or more, followed for decades, to determine effects of use of talcum powder products on risk for ovarian cancer. This is because ovarian cancer is a rare disease and typically takes many years to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type.

Analogy: Bradford Hill states that in some circumstances it would be fair to judge by analogy. Therefore, since some toxic agents such as thalidomide or rubella have been shown to cause birth defects, other drugs or viral exposures may be recognizable as possibly leading to harmful effects to a

fetus. Regarding talcum powder products use and ovarian cancer use: since increased inflammation has been associated with increased ovarian cancer risk, and since talc causes an inflammatory response in tissues, this strengthens the link between talcum powder products use and ovarian cancer risk.

Methods Used for this Review

In performing this evidence review and for purposes of my opinions, I first conducted a review of the relevant literature on the epidemiology of ovarian cancer risk in relation to use of talcum powder products, using the same process I use for systematic review articles I write for my academic work.(60, 65) I triaged articles by title, then by abstract, and finally by complete paper. As I read the epidemiologic literature, I considered the “Bradford Hill” aspects of causal inference(43), as well as causal inference as defined by Rothman(50), and weighed the evidence. My search identified studies that both support and do not support my eventual opinion on whether use of talcum powder products can cause ovarian cancer.

I searched in the PubMed database for research studies published in peer-reviewed, PubMed indexed journals, using the following search terms: (“talc” OR “talcum powder”) AND (“ovarian cancer” OR “ovarian carcinoma”).

The search produced 110 references, of which 7 included meta-analyses (11, 22, 34-38), one was a pooled analysis (39), and 33 were reports of original epidemiologic studies that tested the association between talcum powder products and risk of ovarian cancer.

I did not perform a meta-analysis, because excellent meta-analyses have been recently published,(34, 35) and all of the published meta-analyses showed similar relative risk estimates for use of talcum powder products and risk of ovarian cancer. For all of the reviewed studies, I performed data extraction using a standardized data extraction table (see Tables 1-4). I recorded information on the publication year, study design, number of cases, number of controls (for case-control studies), total sample size (for cohort studies), population type, country, risk estimates, confidence intervals, and the type of ovarian cancer. I also indicated whether dose-response relationships were assessed, method used, and results.

In this report, I provide descriptions of the study methods and main study results including risk estimates (odds ratio, relative risk, or hazard ratio). All studies included control for some confounders and presented the risk estimates with adjustment for the confounders. I present below the results from adjustment with the greatest number of variables.

Epidemiologic Evidence on the Association between Talcum Powder Products Use and Ovarian Cancer Risk

Case-control Studies

Schildkraut *et al.* (2016)(1) investigated the association between body powder use and ovarian cancer in African American women in 11 geographic areas of the U.S. Included were 584 cases and 745 controls, in a population-based study. Cases were identified through state or SEER cancer registries, or through hospital gynecologic oncology departments. Controls were randomly selected from the same populations as the cases. Participants were asked in a phone interview whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Women were classified as “regular users” if they reported using any of these powders at least monthly for at least 6 months, and “never users” otherwise. Regular users were asked about frequency and duration of use; use on genital areas, underwear, sanitary napkins, or diaphragms; and use on non-genital areas. Lifetime number of applications was estimated as number of applications per month times number of months used. Occupational exposure (yes/no) was ascertained for a subset of participants. Use of genital powder was associated with a statistically significant 44% increased risk for ovarian cancer (odds ratio 1.44, 95% CI 1.11-1.86). A dose-response trend was noted: compared with never-users, women who used genital powder less than daily had a 12% increased risk for ovarian cancer, while women who used genital powder daily had a 71% increased risk. The statistical test for trend was significant ($p < 0.01$). Furthermore, a greater number of years used increased risk further: compared with never-users, women who used genital powders for less than 20 years had a 33% increased risk of ovarian cancer, while those who used genital powders for 20 years or more had a 52% increased risk of ovarian cancer. The statistical test for trend was significant ($p = 0.02$). Estimated lifetime number of applications was also related to risk in a dose-dependent manner. Compared with never users, those who used fewer than 3600 genital powder applications had a 16% increased risk for ovarian cancer, while those who used 3600 or

more applications had a 67% increased risk. The statistical test for trend was significant ($p < 0.01$). Risk of both serous and non-serous ovarian cancer increased statistically significantly with any genital powder use by 38% and 63%, respectively (odds ratios, 1.38, 95% CI 1.03-1.85, and 1.63, 95% CI 1.04-2.55, respectively).

Cramer *et al.* (2016) (2) reported on association between genital talc use and risk of ovarian cancer in 2,041 cases of ovarian cancer and 2100 controls. Cases were combined from three case-control studies interviewed in 1992-97, 1998-2002, and 2003-2008. Cases were identified from tumor boards and registries in Eastern Massachusetts and Massachusetts. Controls were identified from the same populations as controls. Interviewers asked participants if they “regularly” or “at least monthly” applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or non-genital areas. Type of powder, age begun, years used, and applications per month were ascertained. Lifetime exposure was estimated by multiplying frequency of applications per month by months used, and talc-years were calculated. Participants were then divided into quartiles according to these variables. Participants were also asked if their partners dusted or sprayed powder to their genital or rectal areas. Condom and diaphragm use were ascertained as potential sources of genital talc exposure. Genital talc use was associated with a statistically significant 33% increased risk of ovarian cancer (odds ratio 1.33, 95%CI 1.16-1.52). Risk decreased with increasing time since last use. There was a clear trend to increasing risk for ovarian cancer with increasing frequency of use: compared with never users, risks for 1-7 days per month, 8-29 days per month, and 30 or more days per month were increased by 17%, 37%, and 46%, respectively, and the trend was statistically significant ($p < 0.0001$). Furthermore, as months per year of use increased, risk increased, and the trend was statistically significant ($p = 0.006$). Risk for serous invasive, endometrioid invasive, and serous borderline were increased with any genital talc use, by approximately 40%, and all were statistically significant. Risks of serous invasive and endometrioid also increased significantly with increased talc-years of use. Risks of serous invasive were increased in both premenopausal and postmenopausal women who used genital products, but the results were only statistically significant in premenopausal women. Premenopausal women and postmenopausal women using hormone therapy had the largest risks associated with talcum powder product use for most types of ovarian cancers.

Wu *et al.* (2015) (3) investigated the associations of risk of ovarian cancer and talcum powder products use and other risk factors. Cases were identified through the SEER population-based University of

Southern California cancer registry. A total of 1,701 patients were included; and 2,319 controls were recruited from the cases' neighborhoods using random selection from population lists. In-person interviews were conducted. To determine use of talcum powder products, women were asked if they ever used talc at least once per month for 6 months or more.⁽⁶⁾ If the response was positive, they were asked whether they had ever used talc in non-perineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm. Questions on talc use included age at first use, frequency of use (times per month) and years of talc use. Use of genital talc for one year or more was associated with a statistically significant 46% increased risk for ovarian cancer (odds ratio 1.46, 95% CI 1.27-1.69). Similar relative risks were seen in non-Hispanic white, Hispanic, and African-American women. A dose-response analysis found that for each 5-year use of genital talc products, risk for ovarian cancer increased by a statistically significant 14% (95% CI 1.09-1.20).

Kurta *et al.* (2012)⁽⁴⁾ published results of a population-based case-control study based in Western Pennsylvania, Eastern Ohio, and Western New York State. A total of 902 cases were enrolled, and 1,802 controls were randomly selected from the general population of those areas. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps. Use of perineal talc increased risk for ovarian cancer by a statistically significant 40% (odds ratio 1.40, 95% CI 1.16–1.69).

Rosenblatt *et al.* (2011) ⁽⁵⁾ published results of a population case-control study set in western Washington that investigated the association between genital powder exposure and risk of ovarian cancer. A total of 812 women with ovarian cancer were identified through a population-based cancer registry and interviewed. A total of 1,313 controls were selected at random from the western Washington population. Sources of genital powder were ascertained, including direct perineal application, use on sanitary napkins and diaphragms, and use of deodorant vaginal spray. For powder use on sanitary napkins and use of vaginal deodorant sprays, the authors recorded the total number of months or years in which these products were used. For use of perineal powder, the investigators recorded the age began and ended, number of weeks or months of use per year, and average days per week used. Study participants were also asked about the types of powder used, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The authors then calculated the lifetime duration of use, and estimated lifetime number of applications. Perineal use of powder was associated with a non-statistically significant 27% increased risk for ovarian cancer (odds ratio 1.27, 95% CI 0.97-

1.66). The risk for borderline ovarian tumors was statistically significantly raised by 55% (odds ratio, 1.55, 95% CI 1.02-2.37), whereas risk for invasive ovarian cancers was increased by a non-statistically significant 27% (odds ratio 1.27, 95% CI 0.87-1.58). Use of powder on either sanitary napkins or diaphragms did not increase risk. Use of vaginal deodorant spray increased risk by a non-statistically significant 15% (odds ratio 1.15, 95% CI 0.85-1.56). None of the dose-response or time variables (years of use, lifetime number of applications, age at first use, age at last use, calendar year of first use, time since first and last uses) showed evidence of increasing relative risk of ovarian cancer with increasing level of exposure to talcum powder products. Similarly, there was no evidence of increased risk for ovarian cancer with increasing dose of powder use on sanitary napkins, or of vaginal deodorant sprays. Use of perineal powder increased risk for mucinous borderline, serous borderline, endometrioid, and other non-mucinous ovarian cancers by 47% to 78%, but none of the odds ratios was statistically significant.

Wu *et al.* (2009) (6) presented results of a case-control study of ovarian cancer with 609 cases and 688 controls. Risk of ovarian cancer among users of talcum powder products in the perineal area was increased by 53% (odds ratio 1.53, 95% CI 1.13-2.09). Risk of serous ovarian cancer was also significantly elevated (odds ratio 1.70, 95% CI 1.27-2.28). A statistically significant trend to increased risk with lifetime numbers of applications was observed. Compared with no use, odds ratios for those with ≤ 5200 , $>5200 - \leq 15,600$, $>15,600 - \leq 52,000$, and $> 52,000$ applications were 1.2, 1.38, 1.34, and 1.99, respectively ($p_{\text{trend}} = 0.0004$).

Moorman *et al.* (2009) (7) published data from a population-based case-control study in White and Black women. In total, 1114 cases and 1086 controls were interviewed. They found no association of genital talcum powder product use and risk for ovarian cancer in Whites (odds ratio 1.04, 95% CI 0.82-1.33), and a non-statistically significant increased risk in Blacks (odds ratio 1.19, 95% CI 0.68-2.09). Neither dose-response nor effects by histologic subtype were addressed.

Merritt *et al.* (2008) (8) published results from an Australian-wide population-based case-control study on talcum powder products and risk of ovarian cancer. Included were 1,576 women with ovarian cancer and 1,509 population-based controls. Women provided information on self-administered questionnaires. They were asked if they had ever used powder or talc in the genital area, on underwear, or on sanitary pads or diaphragms. They were also asked about age at first use and years of talc use in

these areas. Duration of talcum powder use prior to and after surgical sterilization was calculated, and all analyses were limited to the time when the fallopian tubes would have been patent. Use of talc elsewhere was also collected. Ever use of talc in the perineal region was associated with a statistically significant 17% increased risk for ovarian cancer (odds ratio 1.17, 95% 1.01-1.36). The increase was strongest for serous (odds ratio 1.21, 95% CI 1.03-1.44), but was also seen for endometrioid (odds ratio 1.18, 95% CI 0.81-1.70). A statistically significant dose-response trend for years of perineal talcum powder use prior to surgical sterilization was seen for all cases combined ($p=0.021$) and for serous ovarian cancer ($p=0.022$). While not statistically significant, increasing years of use was associated with increased risk of mucinous and endometrioid ovarian cancers.

Mills *et al.* (2004) (9) reported on a population-based case-control study in 22 counties of Central California. A total of 256 cases were recruited from cancer registries and interviewed, and 1,122 population-based controls were randomly selected and interviewed. Women were asked the following about use of talcum powder: use in the genital area, years of use, frequency of use, and total duration of use. Ever use of perineal talc statistically significantly increased risk for ovarian cancer by 37% (odds ratio 1.37, 95% CI 1.02-1.85). There was a statistically significant trend found in the dose-response analysis of frequency of use; women using talc 4-7 times per week had a 74% increased risk for ovarian cancer ($p=0.015$). There was an indication of trend with duration of use up to 4-12 years, although number of years beyond that did not increase risk further. A similar relationship was found for cumulative dose (frequency times duration). Risk of serous ovarian cancer was also statistically significantly elevated (odds ratio 1.77, 95% CI 1.12-2.81).

Ness *et al.* (2000) (10) recruited women with ovarian cancer ascertained from 39 hospitals in Eastern Pennsylvania, Southern New Jersey, and Delaware. A total of 767 cases of ovarian cancer were interviewed, along with 1,367 population-based controls. Women were asked if they ever used talc, baby, or deodorizing powder at least once per month for 6 or more months in their genital or rectal area, on sanitary napkins, on underwear, on a diaphragm or cervical cap, or on non-genital areas. They also were asked about male partner use of talc to the genital area or underwear. Compared with never-users, women who used talc in genital/rectal areas had a statistically significant 50% increased risk for ovarian cancer (odds ratio 1.5, 95% CI 1.1-2.0). Those who used it on sanitary napkins had a statistically significant 60% increased risk for ovarian cancer (odds ratio 1.6, 95% CI 1.1-2.3). Use on underwear increased risk by a statistically significant 70% (odds ratio 1.7, 95% CI 1.2-2.4). Use on a

diaphragm/cervical cap or by a male partner did not increase risk. Among those who used in the genital/rectal or other body areas, there was no evidence of increasing risk with increasing numbers of years of use.

Cramer *et al.* (1999) (11) published results of a population-based case-control study with 563 cases of ovarian cancer and 523 controls. Risk of ovarian cancer among women with perineal talcum powder product exposure was increased 60% compared with non-exposed (odds ratio 1.6, 95% CI 1.18-2.15). Risk of invasive serous ovarian cancer was significantly increased (odds ratio 1.7, 95% CI 1.22-2.39). No dose-response effect, as defined by duration, was seen.

Wong *et al.* (1999)(12) conducted a hospital-based case-control study in Buffalo, NY, comparing 499 patients with ovarian cancer and 755 patients with non-gynecological malignancies. No details were given on how talcum powder product use was ascertained, but women were queried on site of talc use (sanitary napkin vs. genital/thigh area) and duration of use. Compared with non-users, those who used on sanitary napkins or genital/thigh areas had no increase in risk for ovarian cancer. Furthermore, there was no apparent trend toward greater risk with longer duration of use. Finally, there was a non-statistically significant 20% increased risk of serous ovarian cancer with talcum powder product use (odds ratio 1.2, 95% CI 0.7-2.1).

Godard *et al.* (1998)(13) studied risk of sporadic (101 cases) or familial (51 cases) ovarian cancer according to perineal talc use compared with 152 control in Montreal, Canada. Cases were diagnosed at one of two teaching hospitals; controls were randomly selected from the population. Talc use questions were not detailed in the paper, but the variable of “ever” versus “never” perineal use of talc was reported. Women who had ever used perineal talc had a 2.49 times greater risk of developing any ovarian cancer (relative risk 2.49, 95% CI 0.94-6.58, $p=.066$), which was marginally statistically significant. The relative risk for sporadic ovarian cancer was 2.45 (95% CI 0.85-7.07, $p=0.098$), and for familial ovarian cancer it was 3.25 (95% CI 0.85-12.4, $p=.084$).

Green *et al.* (1997)(14) included 824 Australian women with ovarian cancer who were identified through cancer registries, as well as 855 population-based controls. No details were provided on the specific questions posed regarding talc use, but perineal use was ascertained, as well as duration and ages/years used. Women who had ever used talc in the perineal region had a statistically significant 30% increased

risk for ovarian cancer (relative risk 1.3, 95% CI 1.1-1.6). The authors investigated whether a history of surgical sterilization affected this relative risk (the rationale being that women who are surgically sterilized would have lower chance of talc migrating up to the ovaries). They found that compared with women who had neither used talc nor had surgical sterilization, risk was highest among talc users without surgery (relative risk 1.3, 95% CI 1.0-1.7) and lowest among women with a history of tubal sterilization or hysterectomy who had not applied talc to the perineum (relative risk 0.6, 95% CI 0.5-0.84). No dose-response relationship by duration of use was found.

Cook *et al.* (1997) (15) reported on a population-based case-control study including 313 cases of ovarian cancer identified through a cancer registry and 422 population-based controls in Western Washington. Women were queried about storing diaphragms in powder, dusting perineal areas with powder after bathing, powdering sanitary napkins, and using genital deodorant sprays (which may contain aerosolized powder). Women were further asked about duration and frequency of powder application and about types of powder applied. There was a statistically significant 50% increase in risk of ovarian cancer associated with use of any of the genital powder applications (perineal application, sanitary napkins, genital deodorant sprays, diaphragms) (relative risk 1.5, 95% CI 1.1-2.0). The risk was highest, and statistically significant, in those women who dusted perineal areas with powder (relative risk 1.8, 95% CI 1.2-2.9). Compared with never users of genital deodorant sprays, women who used these products for 12 months or less had a relative risk for ovarian cancer of 1.5, while those who used them for more than 12 months had a relative risk of 2.7. Compared with never users of genital deodorant sprays, women who used 500 lifetime applications or less of genital deodorant sprays had a relative risk for ovarian cancer of 1.7, while those who used more than 500 applications had a relative risk of 2.6. Both of these dose-response trends were statistically significant ($p < 0.05$). None of the other types of perineal talcum powder product use showed trends to greater risk with greater estimated duration used or applications. The authors then categorized powders into specific types: cornstarch, talcum powder, baby powder, deodorant powder, and scented body/bath powder (assuming talcum powder was likely a constituent of the latter three as well). Exclusive use of cornstarch, or of deodorizing powder, was not associated with increased risk for ovarian cancer, but the numbers of cases were very small (5 and 9, respectively). Exclusive use of other types of powder increased risk between 20 and 60 percent, but the results were not statistically significant. Risk for serous ovarian cancers was statistically significantly increased by 70% in women who ever used any genital powder (relative risk 1.7, 95% CI 1.1-2.5). The relative risk for

“other tumors” among ever users was 1.8 (95% CI 1.1-2.8), while risks for mucinous or endometrioid tumors were not increased in genital powder users.

Chang *et al.* (1997)(16) reported on the association between talcum powder product use and risk of ovarian cancer in a population-based case-control study in Ontario, Canada. A total of 450 patients with borderline or invasive ovarian cancer and 564 population controls were interviewed. Women were asked about regular talc use and type of talc used, as well about duration and frequency of use. Women were queried about regular application of talc to the perineum and about use of talc on sanitary napkins. Use of cornstarch on the perineum and sanitary napkins was also ascertained. Women with any regular talc exposure had a statistically significant 42% increased risk of developing ovarian cancer (odds ratio 1.42, 95% CI 1.08-1.86). Use of cornstarch was not associated with increased risk, although this was a very uncommon exposure in this study. Use of talc on sanitary napkins increased risk to a lesser degree (odds ratio 1.26, 95% CI 0.81-1.96), as did use of talc only in the perineal area (odds ratio 1.31, 95% CI 1.00-1.73). A dose-response trend was seen: per 10 years of use of talc to the perineal area, risk of ovarian cancer increased by 6% (odds ratio 1.06, 95% CI 0.99-1.14). Frequency of use per month, however, did not show a dose-response trend. Use before and after 1970 showed almost identical odds ratios. Risk was higher prior to tubal ligation/hysterectomy than after either procedure. Risk was increased for all types of ovarian cancer included (invasive, borderline, serous, mucinous, and endometrioid). Only for invasive cancer was the odds ratio statistically significant, likely due to the larger numbers of cases in that category.

Shushan *et al.* (1996)(17) published results of a population-based case-control study in Israel, looking at the association between talcum powder product use and risk of invasive or borderline ovarian cancer. A total of 200 cases, identified through a cancer registry, were interviewed, as were 408 controls selected randomly from the same population. Details of the talcum powder product use on the standardized questionnaire were not provided. Women who reported using talc “moderate to a lot” versus “never or seldom” had twice the risk of developing ovarian cancer, and the result was statistically significant (odds ratio 2.0, $p=0.04$).

Purdie *et al.* (1995)(19) studied the association between talcum powder product use and ovarian cancer risk in 3 Australian states. Cases were recruited from registries at three oncology treatment centers, and controls were chosen randomly from the general population. The details of the interview items on talc

were not provided. Women who used talc around the perineum or abdomen had a statistically significant 27% increased risk for ovarian cancer (odds ratio 1.27, 95% CI 1.04-1.54).

Cramer *et al.* (1995)(18) published results of two case-control studies, in which a total of 450 women diagnosed with ovarian cancer in Boston, MA area hospitals, and 454 controls selected from the general population, were interviewed. Use of talc “in genital hygiene” was associated with a 60% increased risk for ovarian cancer (odds ratio 1.6, 95% CI 1.2-2.1).

Tzonou *et al.* (1993)(28) conducted a hospital-based case-control study in Athens, which included 189 women with ovarian cancer and 200 hospital visitor controls. No information was provided on how talcum powder product use was ascertained, other than that women were interviewed about whether or not they used of talc in the perineal area. There was little evidence of an association: the relative risk for ovarian cancer in those who said “yes” versus “no” to perineal talc use was 1.05 (95% CI 0.28-3.98). However, only 6 cases and 7 controls reported using talc in the perineal area.

Rosenblatt *et al.* (1992)(20) published results of a hospital-based case-control from the Baltimore, MD area. A total of 77 cases of ovarian cancer and 46 controls, who were treated for non-gynecologic/non-malignant diseases, were included. Participants were interviewed about presence and length of genital fiber and respiratory fiber exposure. Fiber exposure was defined as exposure to asbestos, talc, and fiberglass. Dose of exposure was calculated as number of years of each type of genital or respiratory exposures from all sources, and only exposure prior to tubal ligation (for women who had that procedure) was counted. Use of genital talc was associated with a 70% increased risk (odds ratio 1.7, 95% CI 0.7-3.9). Use of talc on sanitary napkins resulted in almost a 5-fold statistically significant increase in risk of ovarian cancer (odds ratio 4.8, 95% CI 1.3-17.8). Talc use on diaphragms tripled risk for ovarian cancer (odds ratio 3.0, 95% CI 0.8-10.8). The odds ratios for these latter two exposures were not statistically significant. Women who had exposure years above the median had more than double the risk of ovarian cancer compared with women with lower exposure years (odds ratio 2.4, 95% CI 1.0-5.8).

Chen *et al.* (1992)(21) interviewed 112 women with ovarian cancer and 224 community controls in China. No information was provided about how women were asked about talcum powder product use prior to 3 years before diagnosis (for cases) and a comparable date in controls. Seven cases and 5

controls reported using “dusting powder” to the lower abdomen and perineum for 3 or more months, giving a relative risk of 3.9 (95% CI 0.9-10.6).

Harlow *et al.* (1992) (22) published a case-control study with 235 cases of ovarian cancer and 239 controls. The authors found a 50% increased risk of ovarian cancer in women who had ever versus never used talcum powder products in the perineal area with marginal statistical significance (odds ratio 1.5, 95% CI 1.00-2.1). Risk of serous cancer was similarly increased (odds ratio 1.4, 95% CI 0.9-2.2). Risk by number of lifetime applications indicated a dose response effect. Compared with no use, odds ratios for those with < 1000, 1000 – 10,000, and > 10,000 were 1.3, 1.5, and 1.8, respectively ($p_{\text{trend}} = 0.09$).

Booth *et al.* (1989) (23) reported on a hospital-based case-control study conducted in 15 hospitals in the UK. A total of 235 cases with ovarian cancer and 451 controls were interviewed and asked about monthly experiences from age 16 to 45 years. Frequency of exposure to perineal talc was ascertained. Compared with never-users, women who used genital talc rarely, monthly, weekly, and daily, respectively, had relative risks for ovarian cancer of 0.9, 0.7, 2.0, and 1.3, respectively, and the trend was statistically significant ($p=0.05$). Cases and controls did not differ by percentage who stored diaphragms in talc.

Harlow *et al.* (1989)(24) interviewed 116 women with serous or mucinous borderline ovarian cancer identified through a Western Washington population-based cancer registry, as well a population-based sample of 158 control women. The authors used an open-ended question asking women to specify the types of powder they used for perineal application after bathing, on sanitary napkins, and on diaphragms. Powder was categorized as baby, deodorizing, other/unspecified talcum, or cornstarch. There was no association between perineal use in general and risk for borderline ovarian cancer, but women who reported using powder on sanitary napkins had a relative risk of 2.2 (95% CI 0.8-19.8) compared with nonusers. Women who used deodorizing powders had a statistically significant relative risk of 2.8 (95%CI 1.1-11.7). No data were presented on frequency or duration of use.

Whittemore *et al.* (1988)(25) included 188 ovarian cancer cases (identified through 7 hospitals in the San Francisco, CA area, and 539 controls (of which approximately half were hospital controls and half were population-based controls). Women were asked whether they had ever use talcum powder on the perineum, on sanitary pads, or on diaphragms, and about frequency and duration of use. Women who

reported using talcum powder to the perineum had a non-statistically significant 45% increased risk for ovarian cancer (relative risk 1.45, 95% CI 0.81-2.60). Use on sanitary pads was associated with a non-statistically significant 38% reduced risk, and use on diaphragms was associated with a non-statistically significant 50% increased risk. The relative risk for ovarian cancer increased with increasing applications of talc per month; relative to nonusers, the relative risk for 1-20 times per month was 1.27, and the relative risk for 20 or more times per month was 1.45. None of these values was statistically significant. The increased relative risk was apparent for women who had never had tubal ligation or hysterectomy, but not for women who had had one of these procedures. Compared with non-users, women with 1-9 years of use had a relative risk of 1.6 (95% CI 1.00-2.57), but women with greater years of use had only a relative risk of 1.11 (95% CI 0.74-1.65).

Hartge *et al.* (1983)(26) provided a brief report on a small hospital based case-control study of ovarian cancer, which included 135 cases and 171 controls from the Washington, DC area. No information was provided on how the talc exposure was ascertained. The authors found that women who reported genital talc use had a relative risk of 2.5 compared with never users (95% CI 0.70-10.0), but this analysis was based on only 7 cases and 3 controls.

Cramer *et al.* (1982) (27) published the first study to look at the association between talcum powder product use and risk of ovarian cancer. This population-based study found an odds ratio of 1.92 (95% CI 1.27-2.89) for ever use of perineal talcum powder products in the perineal area. Dose-response was not addressed.

Summary of Case-control Studies

These 28 case-control studies included population-based and hospital-based studies from a diverse geographic area across the U.S., as well as Australia, Canada, the UK, Israel, Greece, and China. Sample sizes ranged from 77 to 2041 cases, with comparable numbers of controls. Of the 28 studies, 24 found odds ratio greater than 1.1 for ovarian cancer in women who had any perineal exposure to talcum powder products, compared with never users(1-6, 8-11, 13-23, 25-27). Of these 24 odds ratio estimates, 16 were statistically significant (95% confidence intervals excluded 1.0 or p value ≤ 0.05)(1-4, 6, 8-11, 14-19, 27). Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result(13, 20-23, 25, 26). It is

important to note that while the 8 studies did not have statistically significant results, they provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results.(50)

Both population-based and hospital-based studies were represented in the literature on use of talcum powder products and risk of ovarian cancer, and odds ratios/relative risks were similar across the two classes of studies. Earlier studies were less likely to address dose-response relationships, or to investigate effects of talcum powder product use on specific histologic subtypes of ovarian cancer. Most studies were limited to white women; later studies included larger numbers of Black women as well as Asian and Latina women.

The larger, and more recent studies, however, added important information on dose-response relationships and on risk of particular histologic subtypes of ovarian cancer. Many of the 28 studies found evidence of a dose-response effect(1-3, 6, 8, 11, 20, 22, 23, 25). Most often, this took the form of lifetime numbers of applications of talcum powder products or years of use. The later studies determined that some risk of some subtypes, particularly serous ovarian cancer, were more highly related to use of talcum powder products.

Taken together, the case-control studies, conducted over 40 years, provide consistent and replicated evidence of increased risk of ovarian cancer with perineal exposure to talcum powder products, with evidence of a dose-response. They support the conclusion that talcum powder products can cause ovarian cancer.

Prospective Cohort Studies

The Sisters' Study

The Sisters' Study cohort analysis included 135 cases of women with ovarian cancer, 7 cases of fallopian tube cancer, 4 cases of peritoneal cancer, and 8 cases with unknown primary site. (30) Of the total 154 cases, only 96 were confirmed by medical records or death certificate. Women were recruited to the cohort from across the United States from 2003-2009. An analysis of talcum powder products use and ovarian cancer risk, published in 2016, included 41,654 women who reported having at least one ovary

and no history of ovarian cancer at study entry, from among 50,884 women aged 35-74 years at study enrollment with at least one sister who had been diagnosed with breast cancer.

Talcum powder products use for the 12 months prior to study entry was ascertained by self-administered questionnaires. Questions included frequency of genital talcum powder products use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1-3 times/month, used 1-5 times/week, or used more than 5 times/week. Only a dichotomous variable—use/nonuse—was used in the analysis. Ovarian cancer cases were identified by yearly follow-up questionnaires; no updates on talc use were included. The median follow-up of study participants was only 6.6 years.

Contrary to all of the other epidemiologic studies, perineal talc use was associated with a non-statistically significant 27% decreased risk of developing ovarian cancer (hazard ratio 0.73, 95% CI 0.44 - 1.2). Of note, the 95% CI's included 1.2, so the true relative risk in this cohort could have been in the range of the other studies. Use of talcum powder products during ages 10-13 years showed a non-statistically significant 10% increase in risk (hazard ratio 1.1, 95% CI 0.74, 1.7). No data on risk by ovarian cancer subtype were presented.

Women's Health Initiative

In 2014, a report on the use of perineal powder in relation to ovarian cancer risk was published, using a total of 429 cases of women with ovarian cancer from the Women's Health Initiative cohort study.⁽²⁹⁾ Women were aged 50-79 years at study entry, and were recruited from 40 clinical centers across the United States between 1993-1998. While over 93,000 women were enrolled in the Women's Health Initiative cohort, this analysis included only 61,576. The largest number, 20,960, were excluded because they reported previously having had both ovaries removed or did not know whether they had any ovaries at the time of enrollment. Also excluded were 10,622 women with a history of any invasive cancer at enrollment. A further 516 were missing follow-up information. At study entry, women reported use of perineal powder on self-administered standardized questionnaires, in which they were asked if they had ever used powder on their genital areas. Those who responded yes were then asked to indicate if they used them for less than 1 year, 1-4 years, 5-9 years, or 20 or more years. Women who reported ever using a diaphragm were asked if they used powder on the diaphragm, and for what

duration. Women were also asked if they used powder on a sanitary napkin/pad, again with questions about duration. Because of the relatively small number of ovarian cancer cases (429) that occurred during the study, the investigators combined the duration categories into never, 9 years or less, or 10 years or more. The investigators then created one variable by combining the perineal use, diaphragm use, and sanitary napkin use, with duration as the maximum duration for any of the 3 application areas. Cases of ovarian cancer were identified by participants on annual follow-up questionnaires; no updates on talc use were included. Medical records and pathology reports were requested for each self-reported case and were adjudicated by clinic physicians and central cancer adjudicators. A total of 429 cases were included in the analysis.

Ever use of perineal powder was associated with a non-statistically significant 6% increased risk of ovarian cancer compared with never use (hazard ratio 1.06, 95% confidence interval 0.87 - 1.28). Risk of serous invasive cancer was increased by a non-statistically significant 13% (hazard ratio 1.13, 95% CI 0.84 - 1.51). Both of these results, while not statistically significant, are consistent with an association between talcum powder product use and risk of ovarian cancer overall and of serous ovarian cancer.

Nurses' Health Study

The Nurses' Health Study is a cohort established in 1976 that had 307 cases of ovarian cancer at its initial publication in 2000; further data with a total of 210 cases were published in 2008; and an unknown number of cases were analyzed for publication in 2010. The study initially enrolled 121,700 registered nurses between the ages of 30-55 years from across the United States. Use of talcum powder was ascertained on the self-administered 1982 questionnaire only, by asking women if they had ever commonly used talcum, baby powder, or deodorizing powder on their perineal areas. Possible responses were: no, daily, 1-6 times per week, or less than once per week. Women were also asked if they had applied these products to sanitary napkins. "Ever talc use" was classified as ever talc use on either the perineal area or sanitary napkins. Every two years, participants reported health updates; no updates on talc use were included, but self-reported cases of ovarian cancer were adjudicated through medical record reviews. Women were excluded from talcum powder products analyses if they did not complete the information on the 1982 questionnaire, if they reported having had both ovaries removed, if they had had a hysterectomy but did not report whether or not they had at least one ovary remaining, or if they had a history of radiation therapy.

There have been three publications from the Nurses' Health Study on the relationship between talcum powder products and risk for ovarian cancer.(31-33) The first, published in 2000, included 78,630 women, of whom 307 cases of ovarian cancer were diagnosed during a 14 year follow-up period. Ever use of talc was reported by 40.4% of the cohort; 14.5% ever used talc daily.(31)

The risk of ovarian cancer was not statistically significantly associated with epithelial ovarian cancer overall (relative risk 1.09, 95% CI 0.86-1.37), and risk did not increase with increasing frequency of use. Risk of serous ovarian cancer, however, was statistically significantly increased by 40% in women who had ever used talc (relative risk 1.4, 95% CI 1.02-1.91).

The second report from the Nurses' Health Study was in 2008.(32) In this study, 210 cases and a random sample of 600 controls from the Nurses' Health Study were combined with cases and controls from other case-control studies. Among the Nurses' Health Study cases and controls, the relative risk for ovarian cancer was 1.24 (95% CI 0.83-1.83).

Daily use was associated with a 44% increase in risk (relative risk 1.44, 95% CI 0.88-2.37), although neither association was statistically significant. Given that only 210 Nurses' Health Study cases were included, the lack of statistical significance is likely due to this insufficient sample size.

The third Nurses' Health Study report was published in 2010.(33) This report looked at multiple menstrual, hormonal, health habits, and familial risk factors for ovarian cancer; the variable on use of talc to the perineal area was limited to a dichotomous "greater than or equal to once per week vs. less than once per week".

Use of talc one or more times per week compared with less use was not statistically significantly related to risk for epithelial ovarian cancer (relative risk 1.06, 95% CI 0.89-1.28), serous invasive (relative risk 1.06, 95% CI 0.84-1.35), or for other subtypes including endometrioid, or mucinous ovarian cancer.

It is difficult to compare the results of these three Nurses' Health Study publications. The first and third used different categories of use as the referent (comparison) group. The first publication used "never use" as the comparison and found a statistically significant effect for risk of serous ovarian cancer with

any use of talcum powder products. The third publication combined “never use” and “less than once per week” into one referent category. If low frequency use increases risk of ovarian cancer, which is entirely plausible, combining such women with never users will seriously underestimate the true relative risk associated with use of talcum powder products. The second publication found increased risks of total and serous ovarian cancer with use of talcum powder products, but the numbers were small and therefore the results were not statistically significant.

Cohort Studies Analysis

Two of the three cohort studies found small increases in risk of ovarian cancer overall among women who used talcum powder products in the perineal areas. The results were not statistically significant for ovarian cancer overall, however, likely due to insufficient sample size or incomplete ascertainment of talc exposure. The first Nurses’ Health Study publication found a statistically significant association between ever versus never use and risk of serous ovarian cancer. The Sisters’ Study found a reduced risk of ovarian cancer but did not report data by histologic subtype of ovarian cancer. Similar to the Nurses’ Health Study, the Women’s Health Initiative found an increase, albeit non-statistically significant, in risk of serous ovarian cancer in users versus nonusers of talcum powder products.

There were serious limitations to these cohort study analyses. None of the studies were specifically designed to investigate the relationship of talcum powder product use and risk of ovarian cancer. Rather, the cohorts were designed to study a large number of outcomes and a wide variety of exposures. Thus, none of the studies obtained detailed lifetime histories of talcum powder product use, although two did ask about duration of use for current users. None, therefore, was able to accurately measure dose of exposure. The sample sizes (numbers of cases) of most of the cohort study publications were likely too small to be able to detect a relative risk in the order of 1.24 (the value found in the Terry pooled analysis(39)) with reasonable power, especially for different histologic subtypes.

To assess likelihood of inadequate sample sizes in these cohort studies, I used an online calculator: <http://www.openepi.com/SampleSize/SSCohort.htm>. I used WHI data(29) to estimate the cohort sizes needed to determine a true relative risk of 1.24 (i.e. the relative risk from Terry et al pooled analysis(39)) with 50% exposure to talcum powder products in non-cases, and an assumption of 0.5% occurrence of ovarian cancer in unexposed women(66) over 12 years’ follow-up (the mean number of years of follow-

up in the WHI publication). My calculations show that to have sufficient power to identify a statistically significant relative risk of 1.24, the necessary cohort size would be over 140,000. None of the 3 cohorts had this large a sample size for these publications. Sample size ultimately rests on the numbers of cases that occur, rather than the actual cohort size. While the third Nurses' Health Study publication(33)—had a large sample size of cases, the authors' choice to combine never users with less than once per week users could have significantly attenuated the relative risk estimates.

Results of the cohort studies were overall attenuated compared with results of the case-control studies. However, the trend for 2 of the 3 studies was a positive relative risk of talcum powder product use and risk of ovarian cancer. In the Nurses' Health Study, women who used these products had a statistically significant 40% increased risk of developing serous invasive ovarian cancer compared with non-users.(31) In that study, use in the perineal area directly or on sanitary napkins increased risk of ovarian cancer overall by a non-statistically significant 15%.

In the Women's Health Initiative, use of talcum powder products to the genital area (or on sanitary napkins or diaphragm) increased risk overall by a non-statistically significant 6%, and risk of serous invasive ovarian cancer by a non-statistically significant 13%.

The Sisters Study asked only about use of talcum powder product use in the 12 months prior to enrollment; just 14% of the cohort used these products in that period. The cohort included only women at high risk for breast cancer recruited beginning in 2003—this may have been a group of women who were aware of the potential carcinogenic effect of talc, and therefore avoided use. This cohort study found a non-statistically significant 27% lower risk of developing ovarian cancer in users versus non-users. Given the likely 30-50-year latency of ovarian cancer development after exposure to a carcinogen(67), however, these results of the Sisters' Study are not likely reflective of risk from exposure to talcum powder products.

It is important to note that the effect sizes in the Nurses' study and in the Women's Health Initiative were in the same direction as seen in virtually all of the case-control studies.

Therefore, the attenuated results from these cohort studies do not reduce my confidence in the observations from the 28 case-control studies described above.

In summary, while the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, their results as a group do not negate the significant case-control study findings and the significant results of the meta-analyses and the pooled analysis.

Meta-Analyses and Pooled Analyses

I reviewed 7 meta-analyses (11, 22, 34-38) and one pooled analysis (39). All of the meta-analyses, and the pooled analysis, found summary elevated risks for ovarian cancer associated with use of talcum powder products. These elevated relative risks were statistically significant. Although many of the source studies from which they performed their meta-analyses had elevated risks for ovarian cancer with use of talcum powder products, the relative risks or odds ratios were not all statistically significant. I interpret the lack of statistical significance in some source studies as being due to the small sample sizes of many of these studies. I calculated the sample size required for a study in which 40% of controls used talcum powder products, in which there is good power (80%) to detect a relative risk of 1.3, and that had low chance of estimated a particular relative risk by chance (<http://www.openepi.com/SampleSize/SSCC.htm>). The calculation showed that the minimum number of cases and controls would need to be 931 each, for a total sample size of 1862. Almost none of the case-control or cohort studies had sample sizes this large. Lack of statistical significance found in the various studies is likely due to their small sample sizes. For this reason, evaluation of the meta-analyses and pooled analysis, with their larger sample sizes, is critical to understanding the state of epidemiologic evidence linking use of talcum powder products to risk of ovarian cancer.

Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-analysis (R. Penninkilampi, Eslick GD, 2018)

In this, most recent, meta-analysis and systematic review, the authors searched 6 electronic databases, and selected observational studies with at least 50 cases of ovarian cancer.(34) They analyzed the association between ovarian cancer, including specific sub-types, and the following variables regarding talcum powder products: any perineal talc use, long-term (> 10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. Included were 24 case-control studies, with 13,421 ovarian

cancer cases. Also included were three cohort studies, with 890 cases and a comparison of 181,860 person-years [numbers of non-cases multiplied by the years of follow-up]).

The authors found that any perineal talc use was associated with a statistically significant 31% increased risk for ovarian cancer (odds ratio 1.31, 95% CI 1.24-1.39).

There was evidence of a dose-response effect by number of lifetime applications. Women whose lifetime applications totaled less than 3600 had a statistically significant 32% increased risk of developing ovarian cancer (odds ratio 1.32, 95% CI 1.15-1.50), while those whose lifetime applications totaled over 3600 had a statistically significant 42% increased risk for ovarian cancer (odds ratio 1.42, 95% CI 1.25-1.61).

Increased risks were seen for all types of ovarian cancer, as well as specific subtypes: all serous (odds ratio 1.32, 95% CI 1.22-1.43), serous invasive (odds ratio 1.32, 95% CI 1.13-1.54), serous borderline (odds ratio 1.39, 95% CI 1.09-1.78), and endometrioid (odds ratio 1.35, 95% CI 1.14-1.6). For all of these subtypes, the confidence intervals did not include 1.0, and therefore are considered statistically significant and unlikely to be due to chance findings. For other subtypes, the following non-statistically significant associations were seen: all mucinous (odds ratio 1.12), mucinous invasive (odds ratio 1.34), mucinous borderline (odds ratio 1.18), and clear cell (odds ratio 1.02).

The association between ever use of talc and overall ovarian cancer risk was higher in case-control studies (odds ratio 1.35, 95% CI 1.27-1.43) than in cohort studies (odds ratio 1.06, 95% CI 0.90-1.25). However, the results for case-control and cohort studies were similar for serous ovarian cancer. In cohort studies, risk for serous invasive cancer was statistically significantly increased by 25% with any perineal talc use (odds ratio 1.25, 95% CI 1.01-1.55), and in case-control studies, it was statistically significantly increased by 36% (odds ratio 1.05-1.75). There was insufficient information from the cohort studies to calculate the dose-response variable (total lifetime applications).

In my opinion, the results of this 2018 meta-analysis give strong support for an association between perineal talcum powder product use and risk for ovarian cancer. A significant number of the aspects of the causal relationship that Bradford Hill describes in his address are present in these data, including strength, consistency, temporality, and biologic gradient. Bradford Hill did not define his first aspect—

strength—other than to say that the likelihood of causality is greater if the agent causes a “several fold higher” increase in risk in exposed persons. However, for agents like perineal talcum powder products that have such high prevalence of use (over 50% in some populations), the odds ratio/relative risk/hazard ratio for perineal talc use is of great importance for both public health and clinical medicine because it means that perineal talc use causes a significant number of ovarian cancer cases every year.

The corollary example of combined estrogen plus progesterone menopausal hormone therapy and breast cancer risk is helpful here. The Women’s Health Initiative clinical trial showed that this type of hormone therapy increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke).(55) Further examples of relative risks less than 1.5 that have significant public health impact because of high prevalence of exposure in the population or in specific subgroups are shown on pages 26-27.

Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis (Berge W, Mundt K, Luu H, Boffetta P, 2017)

The authors of this meta-analysis performed a systematic search of PubMed, Embase, and Scopus databases(35). After quality assurance and redundancy checks, they included in their analysis 24 case-control studies and 3 cohort studies that reported on the association between talcum powder products and risk of developing ovarian cancer. The main meta-analysis compared ever versus never use of genital talc. Additional analyses looked at use of powder on sanitary napkins and diaphragms. Stratified analyses were conducted for tumor types.

From the meta-analysis, the authors observed a statistically significant 22% increased risk of developing ovarian cancer in women who had ever used genital talc versus never users (relative risk 1.22, 95% CI 1.13-1.30).

Significant results were found for dose-response relationships, both for number of years of use and for number of applications. Each 10-year increase in genital talc use was associated with a 16% increase in

risk for developing ovarian cancer (relative risk 1.16, 95% CI 1.07-1.26). Furthermore, each increase of one application per week was associated with a 5% increase in risk (relative risk 1.05, 95% CI 1.04-1.07).

Risk of serous carcinoma was the only subtype of ovarian cancer for which risk was elevated, and it was statistically significant (relative risk 1.24, 95% CI 1.15-1.34). “Late” exposure, which the authors hypothesized could be less likely to include asbestos, conferred a higher risk (relative risk 1.31, 95% CI 1.03-1.61) than did “early” exposure (relative risk 1.18, 95% CI 0.99-1.37). Neither specific use on a sanitary napkin nor on a diaphragm increased risk. Ever use of genital talc on a diaphragm was associated with decreased risk (relative risk 0.75, 95% CI 0.63-0.88).

The association of talcum powder use with increased risk of ovarian cancer was seen in case-control studies (relative risk 1.26, 95% confidence interval 1.17-1.35) but not in cohort studies (relative risk 1.02, 95% confidence interval 0.85-1.2). Furthermore, hospital-based case-control studies had a higher summary relative risk compared with population-based case-control studies (relative risks 1.34 and 1.24, respectively, both statistically significant).

In my opinion, the results of this meta-analysis are very similar to those of the later one described above, and further support the causal effect on ovarian cancer of talcum powder products applied in the perineal area.

Perineal Use of Talc and Risk of Ovarian Cancer (Langseth, Hankinson, Siemiatycki, Weiderpass, 2017)

In a meta-analysis conducted by some of the researchers who had investigated the epidemiologic research on talc exposure and ovarian cancer risk for IARC, data from 20 case-control studies were combined into a meta-analysis.⁽³⁶⁾ The authors found an overall odds ratio of 1.35 (95% CI 1.26-1.46) for ever- versus never-use of talcum powder products. The authors did not perform dose-response analyses.

Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies. (Huncharek, Geschwind, Kupelnick, 2003)

This meta-analysis included fifteen case-control and two cohort studies that had been published between 1966 and early 2001, and that fit eligibility criteria, including documenting type of talc exposure (e.g. dusting perineum vs. sanitary napkins). The meta-analysis produced a statistically significant relative risk of 1.33 (95% confidence intervals 1.16-1.45) for ever versus never use of talc in the perineal area.(37)

The investigators addressed dose-response in the seven studies with information on years of talc exposure or numbers of talc applications per month. However, the authors combined categories of dose (applications per month) and duration of use (years) into one variable, and treated the dose-response analysis as if dose and duration were measuring the same construct. Their statement of lack of dose-response effect, therefore, is misleading in my opinion. The authors suggest that perhaps talc use has a similar carcinogenic effect as asbestos, and cites research showing that asbestos does not show a clear dose-response effect on risk of mesothelioma.

The authors also separated the results of hospital-based (e.g. both cases and controls from the same hospitals) from non-hospital-based (controls selected from the general population) and found a lower relative risk for ovarian cancer (1.19, not statistically significant) for the hospital-based studies and 1.38 (statistically significant) for population-based studies. The authors state that the hospital-based studies would be more accurate because they eliminate bias from case referral patterns to particular hospitals. However, many of the non-hospital-based studies used population-based case ascertainment (e.g. cancer registries) and selected population-based controls, which also eliminates the potential bias of hospital referral patterns.

Genital Talc Exposure and Risk of Ovarian Cancer (Cramer, Liberman, Titus-Ernstoff, Welch, Greenberg, Baron, Harlow, 1999)

In a paper that presented data for a case-control study of genital talc exposure and risk of ovarian cancer, Cramer et al. presented results of a meta-analysis of previous publications on the relationship between talcum powder product use and risk of ovarian cancer.(11) The authors included results from

14 case-control studies, from which they found a statistically significant combined odds ratio of 1.36 (95% confidence interval 1.24-1.49).

A Meta-Analytical Approach Examining the Potential Relationship between Talc Exposure and Ovarian Cancer (Gross and Berg, 1995)

In a meta-analysis sponsored by the Johnson and Johnson company, Gross and Berg included nine case-control and one cohort study in a meta-analysis, and found that the relative risk for women “exposed” versus “non-exposed” to talc was a statistically significant 1.27 (95% confidence interval 1.09-1.48).(38) Eliminating studies that included non-epithelial ovarian tumors, and studies that did not adjust for potential confounders, the relative risk remained statistically significant (relative risk 1.29, 95% confidence interval 1.02-1.63).

Perineal Exposure to Talc and Ovarian Cancer Risk (Harlow, Cramer, Bell, Welch, 1992)

Harlow and colleagues presented results of a meta-analysis of previous publications on the relationship between talcum powder product use and risk of ovarian cancer (in the same paper in which they presented data on a case-control study of ovarian cancer risk in relation to perineal talcum powder product exposure).(22) The authors included results from 6 case-control studies, from which they found a statistically significant combined odds ratio of 1.3 (95% confidence interval 1.1-1.6).

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls (Terry KL *et al.*, 2013)

This pooled analysis used resources and data from the Ovarian Cancer Association Consortium, including 8 population-based case-control studies with relevant data on talcum powder product use.(39) Six of the studies were conducted in the U.S.(5, 7, 11, 68-70), one in Australia(8), and one in Canada(16). The analysis included 8,525 cases of ovarian, fallopian tube, or peritoneal cancer and 9,859 controls selected from the general population. Five of the studies had previously reported on use of talcum powder product and risk for ovarian cancer (5, 7, 8, 11, 16). To harmonize data on genital powder use across the studies, Terry *et al.* defined genital powder use as any type of powder (talc, baby, deodorizing,

cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area. Study-specific powder questions varied in detail about type and method of application. However, the authors were able to classify women into those who “ever used” genital powders vs. those who “never used” powders in the genital area. The included studies also had extensive data on other suspected risk factors for ovarian cancer that were adjusted for in the analyses. To measure cumulative dose of genital powder use, the authors estimated lifetime number of powder applications by multiplying total months of use by frequency of use per month.

Genital powder use was reported by 25% of controls and 31% of cases. In the pooled analysis, ever use of genital powder was associated with a statistically significant 24% increased risk of ovarian cancer (odds ratio 1.24, 95% CI 1.15-1.33) versus women who never used these products. In contrast, women who had used powders only in non-genital areas had no increase in risk for ovarian cancer. Risk for several subtypes of ovarian cancer was statistically significantly increased in women who had used genital powders. Risk for invasive serous cancer was increased by 24% (1,952 cases; odds ratio 1.24, 95% CI 1.13-1.35). Risk for endometrioid cancer was increased by 20% (568 cases; odds ratio 1.2, 95% CI 1.03-1.4), and risk for clear cell cancer was increased by 26% (327 cases; odds ratio 1.26, 95% CI 1.04-1.52). Risk of serous borderline cancer was increased by 45% (odds ratio 1.45, 95% CI 1.24-1.69). Risk of mucinous cell invasive cancer and mucinous cell borderline cancer were not statistically significantly associated with use of genital powder products (206 cases; odds ratios 1.06, 95% CI 0.82-1.26; and 409 cases; 1.19, 95% CI 0.98-1.43, respectively).

There was a striking similarity in findings across studies, and the statistical test for heterogeneity was not significant ($p > 0.61$). All but one study showed odds ratios greater than 1.0, of which 5 were statistically significant (i.e., the confidence intervals did not contain 1.0).

To assess dose-response effects, the authors categorized participants who had used genital powder into 4 equal groups by lowest to highest level of use (quartiles), and compared their risk for ovarian cancer to that in non-users. A clear dose-response trend was evident. Compared with never users of genital powder, women in quartile 1 had a 14% increased risk for ovarian cancer (odds ratio 1.14, 95% CI 1.00-1.31), women in quartile 2 had a 23% increased risk for ovarian cancer (odds ratio 1.23, 95% CI 1.08-1.41), women in quartile 3 had a 22% increased risk for ovarian cancer (odds ratio 1.22, 95% CI 1.07-

1.40), and women in quartile 4 had a 32% increased risk for ovarian cancer (odds ratio 1.32, 95% CI 1.16-1.52). Slightly higher odds ratios were seen when the cancers were restricted to non-mucinous subtypes (i.e., serous invasive, endometrioid invasive, clear cell invasive, and serous invasive): 1.18, 1.22, 1.22, and 1.37, respectively, for increasing levels of use by quartiles. When all 5 categories were included, the trend was highly statistically significant ($p_{\text{trend}} < 0.0001$).

The authors performed some additional analyses to make sure that the results were not biased. First, they excluded cases and controls who only began to use genital powders after undergoing tubal ligation or hysterectomy (after which powder likely would not migrate to the ovaries). This had no effect on the odds ratios—the increased risks for ovarian cancer remained virtually identical in each quartile. They then looked at effect of genital powder use and ovarian cancer risk by subgroups of women according to other ovarian cancer risk factors. They found no significant interactions between genital powder use and parity, reported history of endometriosis, tubal ligation/hysterectomy, or menopausal status. They did find that the effect of genital powder use was higher in normal/overweight women (odds ratio 1.28, 95% CI 1.17-1.39) than it was in women with obesity (odds ratio 1.14, 95% CI 0.98-1.32).

Finally, the authors looked at associations between genital powder use and ovarian cancer by years of beginning use. They found that the association between genital powder use and ovarian cancer risk was similar for women who started use between 1952 and 1961 (odds ratio 1.36, 95% CI 1.19–1.56), between 1962 and 1972 (odds ratio 1.27, 95% CI 1.11–1.46), and after 1972 (odds ratio 1.31 95% CI 1.15–1.51). However, they observed an attenuated association for women who started genital powder use before 1952 (odds ratio 1.08, 95% CI 0.93–1.25).

The Terry *et al.* pooled analysis provides strong evidence that perineal talcum powder product use causes ovarian cancer. “Strong” here does not pertain to size of the odds ratio/relative risk. Rather, it refers to the fact that the number of cases included was larger than any previous study, the 8 case-control studies included showed similar effect sizes for association of genital powder use and ovarian cancer risk (consistency), the dose-response effect was clear, and there were enough numbers of cases to determine effects on subtypes of ovarian cancer.

Summary of Meta-analyses/Pooled Analysis Results

All of the meta-analyses and the pooled analysis demonstrate increased risk of ovarian cancer in women who used talcum powder products in the genital or perineal area compared with nonusers. The earlier meta-analyses included fewer studies, primarily case-control studies. The most recent meta-analyses included three cohort studies and 24 case-control studies.(34, 35) The summary relative risks were quite consistent across the meta-analyses and the pooled analysis, ranging from 1.22 to 1.4 for any versus no use of perineal talcum powder products. Furthermore, all of the summary results were statistically significant. Importantly, the later meta-analyses(34, 35) and the pooled analysis(39) assessed dose-response relationships, while earlier meta-analyses did not(11, 22, 36), or did so inaccurately(37). These findings of increased risk of ovarian cancer with perineal exposure to talcum powder products shows that the observed associations overall and those for dose-response are robust.

One striking observation across the meta-analyses and pooled analysis is that the total sample sizes (numbers of cases) in all of the meta-analyses and the pooled analysis were sufficient to detect statistically significant relative risks of 1.3 for an overall “exposed” versus “non-exposed” variable with prevalence of 40 percent (see page 48 for a calculation of needed sample size). As shown in Tables 3 and 4, the numbers of cases in the meta-analyses and pooled analysis ranged from 1106 to 14,311, with controls of equal or greater number. All of these, therefore exceed the sample size I estimated that is needed to have statistical power to determine relative risks of 1.3. In contrast, many of the individual case-control or cohort studies did not have large enough samples of cases to have statistical power to determine a relative risk of 1.3.

Asbestos, Fibrous Talc, and Heavy Metals in Talcum Powder Products

It is important to note that talc is not asbestos-free. Talcum powder products contain other, potentially carcinogenic substances; of greatest concern is the presence of asbestos in talc, and the presence of talc with asbestiform fibers (fibrous talc), in these products. The presence of any one of these constituents add to evidence of biologic plausibility that would support the consistent increased risk seen in the epidemiologic studies.

Asbestos can take several forms. Proven carcinogenic forms include serpentine (chrysotile) and amphibole (actinolite, amosite, anthophyllite, crocidolite, and tremolite) minerals.(40) Both serpentine and amphibole asbestos forms are classified by IARC as Class 1 carcinogens(40). In their 2012 report, IARC stated that talc deposits may include tremolite, anthophyllite, and actinolite forms of asbestos(40).

Talc may form true mineral fibers that are asbestiform in habit. This form of talc is also referred to as fibrous talc and classified by IARC as a Class 1 human carcinogen(40). The IARC report also noted that “talc containing asbestiform fibers” is not the same as “talc contaminated by asbestos”(40). The conclusions reached in the 100c monograph about asbestos apply to fibrous talc (40). IARC has classified platy (non-fibrous) talc as a 2B “possible” carcinogen(42).

The primary route of exposure to asbestos is respiratory in the general population, although exposure through drinking water and exposure to hair or clothing of asbestos workers has also occurred (40). For talc, the primary exposures listed by the IARC report are respiratory and perineal (40).

Asbestos has been established as a cause of several types of cancer including epithelial ovarian cancer (40, 41). In order to assess the causal relationship between asbestos and ovarian cancer, I conducted a literature search. My search yielded a total of 26 studies that have investigated the epidemiology of asbestos exposure and risk of ovarian cancer. Two of these were meta-analyses, both published in 2011.(71, 72) One was a pooled analysis of 43 Italian cohorts with high asbestos exposure. (73) In addition, IARC published monographs on the carcinogenic role of asbestos, and conducted a systematic review through 2009 of asbestos and risk of ovarian cancer. (40, 41, 74) IARC concluded that asbestos, fibrous talc, chromium, and nickel are Group 1 human carcinogens.(40) IARC also classified cobalt as a 2B “possible” carcinogen.

Published data as recently as 2014 have shown that present-day talcum powder products include several types of asbestos.(75, 76) Company documents and testimony also provide further evidence of the presence of asbestos, fibrous talc, and heavy metals in talcum powder products.(77, 78) Dr. William Longo tested historical samples provided in litigation. Test results reveal the presence of asbestos in approximately half of the samples tested. Additionally, fibrous talc was found at varying levels in all samples.(79-83)

Finally, I have reviewed the report of Dr. Michael Crowley that discusses the different chemicals added to the fragrance constituents contained in Johnson's Baby Powder and Shower to Shower products (84)Based on his review, he has concluded that these chemicals may contribute to the potential carcinogenicity of talcum powder products.

Therefore, based on the scientific literature and testing results, it is my opinion that the presence of asbestos, heavy metals, fibrous talc, and fragrances are all biologically plausible explanations for talcum powder products causing ovarian cancer.

Biological Mechanisms

Evidence of Migration of Talcum Powder Products (Talc, Asbestos, Other Minerals) to the Ovary and Fallopian Tubes

Clinical and laboratory studies have shown that talcum powder products can migrate to the ovaries and fallopian tubes. An early surgical study in healthy premenopausal women found that inert particles placed in women's vaginas moved to their fallopian tubes within 30 minutes in two of the three patients studied.(85) Henderson et al. found talc particles in 10 of 13 (75%) of ovarian tumors studied using an extraction-replication technique.(86) The findings were replicated 8 years later, with all surgeons removing the ovaries wearing gloves with no talc, to ensure that surgical contamination was not the cause of the observed talc within ovaries.(87) This replication study found talc in all 9 samples studied—3 normal ovaries, 3 cystic ovaries, and 3 adenocarcinomas.

In another relevant clinical experiment regarding migration, the researchers placed 3 ml of ^{90m}Tc-labelled human albumin microspheres in women's vaginas one day before pelvic surgery.(88) Of the 21 women for whom the materials moved up from the cervical area, ovaries and fallopian tubes could be counted separate from the uterus in 14. Of these 14, 9 showed radioactivity in the fallopian tubes and ovaries, and 5 showed no radioactivity. In a pathological study as part of a case-control study of benign ovarian conditions, ovaries from 24 women were tested for presence of talc and asbestos by both electron microscopy and light microscopy.(64) All tested ovaries were found to have talc present. Only half of the 24 women reported a history of perineal talc exposure, which suggests additional routes of exposure to talc, such as inhaled powder. The presence of talc was not due to surgical gloves as all

surgeons wore talc-free gloves in this study. In another study employing microscopy (Raman), the study authors found talc particles in ovarian tissue samples from a woman with known perineal talc exposure that were not visible with other methods.(89)

Another study demonstrated migration of talc evaluated powder on medical gloves used to perform pelvic examinations (with gloved hand inserted into the vagina).(90) This study detected powder in the peritoneal fluid, fallopian tubes, and ovaries the following day after the pelvic examination in women exposed to powdered gloves but almost none in women exposed to unpowdered gloves. The differences between the two groups were statistically significant.

In 2007, Cramer described the presence of talc particles observed in a pelvic lymph node of a 68 year old woman with stage III serous ovarian carcinoma.(91) The authors used scanning electron microscopy to identify plate-like particulates in the 5-10 μm range within the lymph node, and energy dispersive X-ray spectroscopy revealed a magnesium and silicate signature compatible with talc. The authors also noted that talc could migrate through transport of the lymphatic system.

The results of these studies demonstrate talcum powder products can migrate from the perineal area to the ovaries and fallopian tube through both genital tract migration and inhalation. In my opinion it is biologically plausible that talcum powder products can reach the ovaries via migration from the perineum and via inhalation into the lungs, blood stream, and lymphatic system.

Inflammation in the Causal Pathway between Talcum Powder Product Use and Ovarian Cancer Development

The literature suggests that a likely pathway through which use of talcum powder products increases risk of ovarian cancer is through talc-induced inflammatory response.(92) As described above, it is well supported that talc can migrate through the female genital tract and settle in the area of the ovaries, fallopian tubes, and peritoneum (64, 86-88, 91, 93). Increased blood levels of biomarkers of inflammation have been linked to increased risk for ovarian cancer. A recent meta-analysis of 8 cohort studies found that women with high blood levels of c-reactive protein (a marker of increased systemic inflammation) had almost double the risk of developing ovarian cancer compared with women with low levels.(94)

Further evidence of the inflammation mechanism comes from studies which evaluate anti-inflammatories, like aspirin and NSAIDs, and reduction of risk of ovarian cancer. A pooled analysis of case-control studies published in 2014 showed that long-term daily use of aspirin (which blocks inflammation) decreased risk of ovarian cancer (odds ratio = 0.91; 95% CI = 0.84-0.99). Similar, but not statistically significant, results were shown for use of other nonsteroidal anti-inflammatory medications.⁽⁹⁵⁾ A 2018 meta-analysis found an 11% reduced risk of ovarian cancer with aspirin use (relative risk 0.89, 95% CI 0.83-0.95).⁽⁹⁶⁾ Aspirin and other nonsteroidal anti-inflammatory medications inhibit the inflammation-mediating enzyme, COX-1⁽⁹⁵⁾; COX-1 is frequently overexpressed in ovarian cancer tissue.^(97, 98)

Chronic inflammation may result in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis.⁽⁹²⁾ Factors related to the inflammation of the ovarian surface and tubal epithelium, such as incessant ovulation, endometriosis, and pelvic inflammatory disease, provide further evidence of inflammation and ovarian carcinogenicity. ⁽⁹⁹⁻¹⁰¹⁾

Talc exposure has also been linked to increased inflammation. It can induce granulomas and other inflammatory responses in vivo.^(102, 103) Injected into the pleural cavity to treat pneumothorax, talc stimulates an intra-pleural inflammatory reaction that causes pleural fibrosis and scarring, leading to obliteration of the pleural space and prevention of recurrent pneumothoraces.⁽¹⁰⁴⁾ In humans, elevated interleukin 8 (a chemotactic cytokine) occurs after pleural injection of talc.⁽¹⁰⁵⁾ In a study of over 227 patients treated with talc pleurodesis; about half received small particle talc, and half received large-particle talc. Patients who received small particle talc had significantly higher proinflammatory cytokines, particularly interleukin 8, in pleural fluid and serum after talc application.⁽¹⁰⁶⁾ In animal models, injection of talc into the pleura can cause local and systemic inflammatory responses⁽¹⁰⁷⁾ including elevated inflammation-related biomarkers c-reactive protein and interleukin 8⁽¹⁰⁸⁾ as well as VEGF, and TGF-beta.⁽¹⁰⁹⁾ This type of inflammation can induce neoplastic changes.⁽¹¹⁰⁾

Additional Evidence of Biological Mechanisms

Exposing human ovarian stromal and epithelial cells to talc resulted in increases reactive oxygen species (oxidative stress), cell proliferation and neoplastic transformation of cells.⁽¹¹⁰⁾ Similarly, in a recent *in*

vitro study by Fletcher et al., talc was applied in different concentrations, for varying numbers of hours, to epithelial ovarian cancer cell lines and normal ovarian epithelial cells.(111) As early as 24 hours post-treatment, they found increases in mRNA (gene expression) of pro-oxidant enzymes iNOS and MPO in talc-treated epithelial ovarian cancer cells and normal ovarian cells, compared with non-treated controls. Marked decreases in several antioxidant enzymes in talc-treated cells were also seen. This study supports the role of talc in inducing oxidative stress, providing a molecular basis for epidemiologic studies demonstrating an increased risk of ovarian cancer with perineal talcum powder product exposure.(111-113) Another *in vitro* study found that talc induced a biological effect by enhancing CA-125 in ovarian cancer cells and in normal cells.(114)

Talc application to human mesothelial cells in cell culture has also been shown to increase gene expression in 30 genes that are relevant to carcinogenesis, and asbestos application increased gene expression in over 200 genes.(115) In the same study, asbestos application to human ovarian epithelial cells increased gene expression in two genes at 8 hours and 16 genes at 24 hours. Many of the expressed genes are relevant to the carcinogenic process. Results from this experimental study show that talc causes a statistically significant increase in gene expression in mesothelial cells in several genes related to carcinogenesis, including activating transcription factor 3 (ATF3), which controls production of several markers of inflammation.(115)

Asbestos, which has been found in talcum powder products, has been classified by IARC as a known ovarian carcinogen after a systematic review of the epidemiological and biological science.(40) Two meta-analyses and one pooled analysis have addressed the association between asbestos exposure and risk of ovarian cancer.(71-73) The studies of asbestos and ovarian cancer were typically studies of cohorts with high levels of occupational or home asbestos exposure, and comparisons were made to the general population as controls. The most recent meta-analysis found that women exposed to asbestos had a relative risk dying of ovarian cancer of 1.77 (95% CI 1.37-2.28) compared with unexposed populations(71). The other meta-analysis found that women exposed to asbestos had a relative risk of developing or dying of ovarian cancer of 1.75 (95% CI 1.45-2.10) compared with unexposed women(72). An additional four cohort studies (73, 116-119), which were published after the date of the most recent meta-analysis(71),as well as the pooled analysis(73) found similar elevated risks of ovarian cancer in women with asbestos exposure.

IARC also lists mechanisms through which asbestos can cause cancer including: impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, and resistance to apoptosis.(41) Asbestos is another biologically plausible explanation for talcum powder products causing ovarian cancer.

It is my opinion, based on these studies, that talc and asbestos induce inflammation which results in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis. This adds to the weight of evidence and provides a plausible biological explanation for the association between genital talcum powder product use and ovarian cancer.

Another line of experiments in support of the biologically plausible mechanism for talcum powder products causing ovarian cancer were conducted in animals. A study with female rats showed that talc is absorbed through the pleural surface and rapidly disseminated throughout internal organs and lymph nodes.(120) Henderson et al found that talc placed in the uteruses or vaginas of female rats moved to the animals' ovaries by four days post-administration.(121)

In another study, exposure of rat ovaries to talc led to cyst formation and epithelial changes.(122) A methodology study discovered that talc caused superoxide anion generation and release from mouse macrophages.(123)

Animal experiments conducted by the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services are highly relevant to the role of talc in carcinogenesis. An NTP rat study provided important "signal " information of talc toxicity relevant to talc and development of ovarian cancer.(124) In an inhalation study, male and female F344/N rats were exposed to daily talc aerosols of non-asbestiform talc, with appropriate controls. NTP concluded that there was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung, and benign and malignant pheochromocytoma of the adrenal gland. The NTP also concluded that there was some evidence of carcinogenic activity of talc in male F344 /N rats based on an increased incidence of benign and malignant pheochromocytoma of the adrenal gland.

In my opinion, these animal studies further demonstrate that talcum powder products and its attendant inflammation can induce carcinogenesis. This provides further evidence of a biologically plausible mechanism supporting causation of ovarian cancer from the use of talcum powder products.

Summary of Findings: Weight of the Evidence/Bradford Hill Analysis

The summary relative risk estimates from the most recent meta-analyses(34, 35) and the pooled analysis(39) indicate that women who have ever used talcum powder products in the perineal/genital areas (including use of sanitary napkins, diaphragms, underwear, and direct application) have approximately 22-31% increased risk of developing ovarian cancer compared with never-users.

This review of the association between talcum powder products in the perineal/genital area produced several clear findings. Below, they are outlined according to the aspects of causality as described by Bradford Hill.(43) The epidemiologic evidence in total, along with the biological and pathological evidence, fits virtually all of the Bradford Hill aspects for causation, namely: the strength of the association, consistency across populations, specificity, temporality, experiment, biologic gradient (dose-response), plausibility, coherence, and analogy.

Strength of the association and statistical significance: The meta-analyses and pooled analysis showed that risk of ovarian cancer among ever users of talcum powder products is 22-31% higher than in women who never used these products. A total of 28 case-control studies, 3 prospective cohort studies, 2 meta-analyses, and one pooled analysis were reviewed in depth. The meta-analyses found a statistically significant 24 – 25% increased risk of developing serous ovarian cancer—representing 52% of epithelial ovarian cancer cases(125) —in women who had ever used talcum powder products compared with never-users. The pooled analysis, which included data from 5 previously published and 3 unpublished case-control studies, found similar statistically significant increased risks for overall epithelial ovarian cancer and serous ovarian cancer (24% and 20%, respectively). Thus, when combining these studies through meta-analyses, the totality of the evidence shows a statistically significant increased risk of ovarian cancer with use of perineal talcum powder products. Viewed in the context of the high consistency of the study results across time, diverse study populations, and strong study

designs, bias and chance as explanation for the increased risk are unlikely. Further, my confidence in the reliability of the data on magnitude of the risk is enhanced. Therefore, my analysis of these studies strongly supports a causal association and, given the high prevalence of use of talcum powder products in this population, these levels of risk present a clinically significant public health concern. I placed high weight on this aspect of determination of causality.

Consistency of the association: Across the case-control and cohort studies, the association between use of talcum powder products and risk of ovarian cancer was highly consistent. As indicated above, the case-control studies included population-based and hospital-based studies from a diverse geographic area across the U.S., as well as Australia, Canada, the UK, Israel, Greece, and China. Of the 28 studies, 24 found odds ratio greater than 1.1 for ovarian cancer in women who had any perineal exposure to talcum powder products, compared with never users (1-6, 8-11, 13-23, 25-27). Of these 24 odds ratio estimates, 16 were statistically significant (95% confidence intervals excluded 1.0 or p value ≤ 0.05). Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result. Furthermore, the increased risk of ovarian cancer with use of talcum powder products has been seen in various race/ethnic groups as well as in diverse geographic areas around the world. While the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, these studies were not well designed to determine true risk for ovarian cancer and perineal talc use. Therefore, their results as a group do not negate the significant case-control study findings and the significant results of the meta-analyses and the pooled analysis.

The most recent and comprehensive meta-analysis by Penninkilampi *et al.*, assessed consistency across the studies included in their analysis by measuring heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity.(34) They then quantified the degree of heterogeneity using the I^2 statistic. The I^2 statistic represents the fraction of the total variability across studies that is due to heterogeneity. The authors categorized I^2 values of 25%, 50%, and 75% as corresponding to low, moderate, and high degrees of heterogeneity, respectively, which is typical for meta-analyses.(126) The authors found that there was no heterogeneity in the relative risk estimates for exposure to talcum powder products in the perineal area, or on diaphragms or sanitary napkins. Even though the 95% confidence intervals contained 1.0 in the cohort studies, given the clearly increased relative risk across the case-control

studies, the trend toward increased risk in two of the three cohort studies, and the results from the Penninkilampi et al. meta-analysis, it is my opinion that this did not occur by chance but is, in fact, a true causal relationship.

The consistency across studies, led by many investigators, using different study designs, and in diverse ethnic, racial, and geographic populations over a period of nearly 35 years weighs heavily as to the consistency and reliability of the data in favor of a causal risk. Accordingly, I placed significant weight on this factor in my causation analysis.

Specificity of the association: Use of talcum powder products is strongly associated with epithelial ovarian cancer. Analyses by histologic subtype of epithelial ovarian cancer found that serous ovarian cancer appeared to be most strongly and consistently related to talc exposure, although the pooled case-control project found associations some other subtypes of ovarian cancer. Mucinous cancers have been consistently found to be unrelated to use of these products. Therefore, the specificity aspect is present for epithelial ovarian cancer and certain subtypes. However, because many carcinogens have been shown to cause diverse and nonspecific morbidities, such as smoking, I weighed this aspect moderately in my causal analysis as compared to other Bradford Hill factors.

Temporality: The epidemiologic studies that looked at lifetime talcum powder product use supported that exposure to these products predated the diagnosis of ovarian cancer. I did not find any evidence of 'reverse causation', e.g., using talcum powder products to alleviate symptoms associated with ovarian cancer, nor do any investigators report finding reverse causation. Importantly, symptoms related to ovarian cancer (bloating, increased abdominal size, abdominal pain, pelvic pain, difficulty eating, feeling full quickly)(127) are not vaginal or perineal in origin, and would be unlikely to induce women to increase use of talcum powder products. The finding of temporality is an important component in the causal analysis and, as such, I place great weight in its applicability to the determination of causality.

Biologic gradient/ dose-response: The earlier studies were less likely to address dose-response associations. The larger, and more recent studies, however, collected important data that inform dose-response relationships. Many of the 28 case control studies found evidence of a dose-response effect. Most often, this took the form of lifetime numbers of applications of talcum powder products or years of use. Thus, while there were studies that did not look for or find a dose-response, the body of

literature when taken as a whole does indicate a dose-response effect. Some studies did not gather detailed dose data such as frequency of use or length of use. Others gathered either frequency of the use or duration of use, but not both. As with smoking, ascertainment of frequency x duration of exposure (cumulative exposure) is an optimal metric to determine true dose-response effects. The meta-analyses and the pooled analysis also found evidence of relationships between increasing amount of exposure to talcum powder products in the perineal/genital area (including frequency, years of use, and estimates of lifetime applications) and increased risk of developing epithelial ovarian cancer (i.e., dose-response relationships). Thus, the studies that accurately determined use of talcum powder products revealed evidence of dose-response effects. When present, the finding of a biologic gradient/dose-response is helpful in determining causation. The findings within the study data, particularly meta-analyses and the pooled analysis, thus, supports my causal analysis and I placed significant weight on this factor.

Plausibility: In my consideration of whether talcum powder products can cause cancer, I considered the data for biologically plausible mechanisms by which exposure to talc could result in ovarian cancer. In that regard, I assessed data and determined that talcum powder products can migrate from the perineum through the female genital tract to the ovaries; talcum powder products are found in ovarian and fallopian tube tissues; talcum powder products can induce an inflammatory response; and because of the inflammatory response, malignant transformation can occur. Support for these finding comes from reliable, peer-reviewed scientific literature which indicates that talcum powder products can migrate from the perineum up the genital tract to the fallopian tubes and ovaries and become imbedded in the ovarian tissue. Thus, it is biologically plausible that genital exposure to talcum powder products can result in exposure to the ovaries.

Data also plausibly indicates that inhalation of talcum powder products can result in exposure leading to cancer, including mesothelioma. Studies also show that talcum powder products can be absorbed and transported via the lymphatic system or blood stream. Therefore, inhalation of talcum powder products could result in similar ovarian exposure. Published scientific data shows that talc reaches the ovary and becomes imbedded in the ovarian tissue. There are reliable data to support that talc induces an inflammatory response which mediates oxidative stress, release of cytokines and resulting genotoxicity which can induce malignant transformation. Further, the presence of asbestos and other constituents in

the talcum powder products such as asbestos, heavy metals, and fragrance have been shown to induce cancer by similar mechanisms.

While I have considered the data that do not support the plausibility of talcum powder products' carcinogenicity, otherwise overwhelming and reliable evidence indicates that there are biologically plausible mechanisms by which talcum powder products can induce ovarian carcinogenicity. Talc and its constituents can reach the ovaries, induce an inflammatory response that leads to genotoxicity and to development of ovarian cancer. While this mechanism of carcinogenicity is not proven, it is highly biologically plausible based on the present scientific information and understanding. Therefore, I place significant weight on this aspect of determination of causality.

Coherence: The cause-and-effect interpretation of the data on talcum powder product use and risk of ovarian cancer clearly do not significantly conflict with the known facts about the natural history and biology of the disease. Increased inflammation has been linked to risk of ovarian cancer, and talc and other contents of talcum powder products elicit inflammatory responses within areas of the body in which they have been found (i.e. ovary, peritoneum, lymph nodes, etc.). By analogy, a similar mechanism has been reported by which asbestos causes ovarian cancer. These mechanisms are consistent with one another and the accepted understanding of the role of inflammation in carcinogenesis. While these factors support a causal association and my opinions in this regard, I do not weigh them quite as heavily as the strength and consistency of the association.

Experiment: As discussed above, the evidence from randomized controlled trials can provide strong support to observational evidence. However, here, randomized controlled trials are neither feasible nor ethical, similar to smoking and lung cancer. This is because ovarian cancer is a rare disease and typically takes decades to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type. Furthermore, the studies involving migration of talc, the inflammatory process and its association with carcinogenesis all contribute in a compelling manner to the causal analysis. While there are experimental data supporting causation from cell studies and animal models, given the inability to conduct experimental studies in humans to test effects of talcum powder products on ovarian cancer development, there are no human experimental data. Despite this, data from reliable observational studies as described in this

report strongly support causation. Therefore, I placed slight weight to this aspect of determination of causality.

CONCLUSION

In conclusion, it is my professional opinion, stated to a medical and scientific degree of certainty, that based on the totality of the evidence, which includes epidemiological, biological, pathological and mechanistic data, perineal use of talcum powder products can cause ovarian cancer.

Tables: Epidemiological Studies of Talcum Powder Product Use and Risk of Ovarian Cancer

Table 1: Case-Control Studies

Study	Country	No. Cases	No. Non-cases	Source of participants	Odds Ratio All Ovarian Ca, Any Perineal Talc Use (95% CI)	Odds Ratio Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-response?
/Schildkraut 2016 (1)	U.S.	584	745	Population	1.44 (1.11-1.86)	1.38 (1.03-1.85)	Yes, OR's: < 3600 apps 1.16 ≥ 3600 apps 1.67 $p_{trend} < 0.01$
Cramer 2016 (2)	U.S.	2041	2100	Population	1.33 (1.16-1.52)	1.42 (a) (1.19-1.69)	Yes > 24 talc-years: OR 1.49 $p_{trend} = 0.02$
Wu 2015 (3)	U.S.	1701	2391	Population	1.46 (1.27-1.69)	Not addressed	Yes, per 5-years talc: OR 1.14 (95% CI 1.09-1.20)
Kurta 2012 (4)	U.S.	902	1802	Population	1.4 (1.16-1.69)	Not addressed	Not addressed
Rosenblatt 2011 (5)	U.S.	812	1313	Population	1.27 (0.97-1.66)	1.47 (borderline) (0.84-2.56) 1.01 (invasive) (0.69-1.47)	No (lifetime number of apps, years of use)
Wu 2009 (6)	U.S.	609	688	Population	1.53 (1.13-2.09)	1.70 (1.27-2.28)	Yes, lifetime apps OR: ≤5200: 1.20 >5200 to ≤15600: 1.38 >15,600 to ≤52000: 1.34 >52000: 1.99

							$p_{trend} = 0.0004$
Moorman 2009 (7)	U.S.	1114	1086	Population	Whites: 1.04 (0.82- 1.33) Blacks: 1.19 (0.68- 2.09)	Not addressed	Not addressed
Merritt 2008 (8)	Australia	1576	1509	Population	1.17 (1.01- 1.36)	1.21 (1.03-1.44)	Yes, OR: None 1.0 > 0-10 yrs 1.13 > 10-25 yrs 1.08 > 25 yrs 1.29 $p_{trend} = 0.02$ (similar stat sign trend for serous)
Mills 2004 (9)	U.S.	256	1122	Population	1.37 (1.02- 1.85)	1.77 (1.12-2.8)	No (freq X dur), OR Never 1.0 Q1 1.03 Q2 1.81 Q3 1.74 Q4 1.06 $p_{trend} = 0.05$
Ness 2000 (10)	U.S.	767	1367	Population	1.5 (1.1-2.0)	Not addressed	No (duration only)
Cramer 1999 (11)	U.S.	563	523	Population	1.60 (1.18 - 2.15)	1.38 (borderline) (0.82, 2.31) 1.70 (invasive) (1.22, 2.39)	Yes, lifetime apps when fallopian tubes patent: OR < 3000: 1.54 3000- 10,000: 1.72 >10,000: 1.80
Wong 1999 (12)	U.S.	499	755 (non- GYN cancer patients)	Hospital	0.92 (.24-3.62)	1.2 (0.7-2.1)	No (duration only)

Godard 1998 (13)	Canada	170	170	Population	2.49 (0.94- 6.58)	Not addressed	Not addressed
Green 1997 (14)	Australia	824	855	Population	1.3 (1.1-1.6)	Not addressed	No (duration only, data not shown)
Cook 1997 (15)	U.S.	313	422	Population	1.5 (1.1-2.3)	1.70 (1.1-2.50)	No (cumulative lifetime days)
Chang 1997 (16)	Canada	450	564	Population	1.42 (1.08- 1.86)	1.34 (0.96-1.85)	No (frequency or duration)
Shushan 1996 (17)	Israel	200	408	Population	2.0 (p=0.04)	Not addressed	Not addressed
Cramer 1995 (18)	U.S.	450	454	Population	1.6 (1.2-2.1)	Not addressed	Not addressed
Purdie 1995 (19)	Australia	824	860	Population	1.27 (1.04- 1.54)	Not addressed	Not addressed
Tzonou 1993 (28)	Greece	189	200	Hospital	1.05 (0.28- 3.98)	Not addressed	Not addressed
Rosenblatt 1992 (20)	U.S.	77	46	Hospital	1.7 (0.7-3.9)	Not addressed	Yes: \geq 37.4 years vs. < 37.4 years: OR 2.4
Chen 1992 (21)	China	112	224	Population	3.9 (0.9- 10.63)	Not addressed	Not addressed
Harlow 1992 (22)	U.S.	235	239	Population	1.5 (1.0-2.1)	1.4 (.9-2.2)	Yes, lifetime applications, OR: < 1000: 1.3 1000- 10,000: 1.5 > 10,000: 1.8 $p_{trend} = 0.09$
Booth 1989 (23)	U.K.	235	451	Hospital	Daily 1.3 (0.8-1.0) Weekly 2.0 (1.3- 3.4)	Not addressed	Yes, RR: Never 1.0 Rarely 0.9 Monthly 0.7 Weekly 2.0 Daily 1.3 $p_{trend} = 0.05$

Harlow 1989 (24)	U.S.	116 border- line only	158	Population	1.1 (0.7-2.1)	Not addressed	Not addressed
Whittemore 1988 (25)	U.S.	188	539	Hospital + population	1.45 (p=0.06)	Not addressed	1-20 applications/ mo RR 1.27 (0.82-1.96) > 20 apps/mo RR 1.45 (0.94-2.22) No p _{trend} provided
Hartge 1983 (26)	U.S.	135	171	Hospital	2.5 (0.7-10.0)	Not addressed	Not addressed
Cramer 1982 (27)	U.S.	215	215	Population	1.92 (1.27- 2.89)	Not addressed	Not addressed

Table 2: Prospective Cohort Studies

Study Year Published	Country	No. Cases	No. Non-cases	Baseline Age	Years of Follow-up	RR All Ovarian Ca, Any Perineal Talc Use (95% CI)	RR Serous Invasive Ovarian Ca, Any Perineal Talc Use	Dose-response
Sister Study Gonzalez, 2016 (30)	U.S.	154	41,500	54.8	Median 6.6 years	0.73 (0.44-1.21)	Not addressed	Not addressed
Women's Health Initiative Houghton, 2014 (29)	U.S.	429	61,147	63.3	Mean 12.4 years	1.06 (0.87-1.28)	1.13 (0.84-1.51)	No (< 9 vs. 10+ years); no frequency data collected
Nurses Health Study Gertig, 2000 (31)	U.S.	307	78,323	36-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.09 (0.86-1.37) (ever use perineal talc vs. never use)	1.40 (1.02-1.91)	No (only frequency data collected, no duration data)
Nurses Health Study Gates, 2008 (32)	U.S.	210	600	36-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.24 (0.83-1.83) (≥ 1 /wk vs. < 1/wk)	1.48 (0.82-2.68) (≥ 1 /wk vs. < 1/wk)	Yes: RR's < 1/wk 0.98 1-6/wk 1.01 > 6/wk 1.44
Nurses Health Study Gates, 2010 (33)	U.S.	797	78,323??	6-61 years in 1982 (year of talcum powder product	Not provided	1.06 (0.89-1.28) (≥ 1 /wk vs. < 1/wk)	1.06 (0.84-1.35)	Not addressed

				use data collected)				

Table 3: Meta-analyses

Study	Number of Studies	Number of Cases	Relative Risk All Ovarian Ca, Any Perineal Talc Use (95% CI)	Relative Risk Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-Response
Penninkilampi 2018 (34)	27	14,311	1.31 (1.24-1.39)	1.32 (1.22-1.43)	Yes: OR 1.32 for < 3600 applications; OR 1.42 for > 3600 applications
Berge 2017 (35)	27	Not provided, should be same as Penninkilampi above	1.22 (1.13–1.30)	1.24 (1.15–1.34)	Yes for duration and frequency: 1) RR per 10-year use 1.16 (95% CI 1.07-1.26); 2) RR per weekly use 1.05 (95% CI 1.04-1.07)
Langseth 2008 (36)	20	Not provided	1.35 (1.26-1.46)	Not addressed	Not addressed
Huncharek 2003 (37)	16	5260	1.33 (1.16-1.45)	Not addressed	No summary estimates calculated. Dose response addressed in 9/16 source studies: no dose-response apparent
Cramer 1999 (11)	14	3834	1.4 (1.2-1.5)	Not addressed	Not addressed
Gross 1995 (38)	10 (N=5 studies with adjusted data and limited to	1509	1.29 (1.02-1.63)	Not addressed	Not addressed

	epithelial ovarian cancers)				
Harlow 1992 (22)	6	1106	1.3 (1.1-1.6)	Not addressed	Not addressed

Table 4: Pooled Analysis

	Number of Studies	Number of Cases	Odds Ratio All Ovarian Ca, Any Perineal Talc Use (95% CI)	Odds Ratio Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-Response All Ovarian Cancer
Terry 2013 (39)	8	8,525	1.24 (1.15– 1.33)	1.24 (invasive) (1.13–1.35)	Yes. OR (95% CI) by quartiles of lifetime applications vs. never use, non-mucinous cases only: Q1 1.18 (1.02-1.36) Q2 1.22 (1.06-1.41) Q3 1.22 (1.06-1.40) Q4 1.37 (1.19-1.58)

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11. Deposition Transcript & Exhibits - John Hopkins (8/16/18, 8/17/18, 10/26/18, 11/5/18)
12. Deposition Transcript & Exhibits - Joshua Muscat (9/25/18)
13. Deposition Transcript & Exhibits - Julie Pier (9/12/18, 9/13/18)
14. Deposition Transcript & Exhibits - Linda Loretz (7/17/18, 10/1/18, 10/2/18)
15. Deposition Transcript of Alice Blount, April 2018
16. Deposition Transcript of Patricia Moorman (Ingham)
17. Expert Report of Jack Siemiatycki
18. Fair warning TalcDoc 15
19. Fair warning TalcDoc 5 - Exhibit 113 (JNJNL91_000022019)
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EXHIBIT A

Curriculum Vitae

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EDUCATIONAL BACKGROUND

Residency, Primary Care Internal Medicine, 6/92, University of Washington School of Medicine, Seattle, WA
M.D., 6/89, New York Medical College, Valhalla, NY
Ph.D. in Epidemiology, 12/82, University of Washington, Seattle, WA
M.A. in Medical Sociology, 6/76, State University of New York at Buffalo,
B.A. in Sociology, 1/74, Boston University, Boston, MA

PROFESSIONAL POSITIONS

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA
Director, FHCRC Prevention Center (2002 - 2012)
Full Member (2001 - present)
Associate Member (1997 – 2001)
Assistant Member (1996 - 1997)
Senior Staff Scientist, Associate in (1983 – 1985; 1992 - 1996)
Department of Epidemiology, University of Washington School of Public Health, Seattle, WA
Research Professor (2003 -)
Research Associate Professor (1999 – 2003)
Research Assistant Professor (1996 - 1999)
Clinical Instructor (1992 - 1996)
Department of Medicine, Division of Geriatrics
Adjunct Research Professor (2003 -)
Adjunct Research Associate Professor (1999 - 2003)
Department of Medicine, Division of General Internal Medicine
Clinical Instructor (1992 – 1996)
Clinical Nutrition Research Unit, University of Washington, Seattle WA
Affiliate Investigator (1996 – present)
Harborview Medical Center, Adult Medicine Clinic, Seattle, WA
Attending Physician (1992 - 1995)
University of Washington, Women's Primary Care Clinic, Seattle, WA
Attending Physician (1996)

HONORS and TRAINEESHIPS

- American College of Sports Medicine Citation Award, 2012
- McDougall Mentoring Award, Fred Hutchinson Cancer Research Center, 2011
- Komen for the Cure Scientific Advisory Council/Komen Scholars, 2010-2012
- University of Washington Roger E. Moe Award for Translational Research 2009
- The Joan P. Liman MD Award, Recipient, New York Medical College, 1989
- National Institute for Dental Research, Fellowship Award in Behavioral Dental Research, 1983
- National Cancer Institute Traineeship, 1980-1982

- University of Washington Public Health Traineeship, 1978-1979

PROFESSIONAL ACTIVITIES

Committee Memberships and Academic Consulting

- 2018 U.S. Dept. Health and Human Services Physical Activity Guidelines Advisory Committee, 2016-2018
- Member, External Advisory Board, Pennington Biomedical Research Center, Louisiana, 2018
- Reviewer, NIEHS Sisters Study, 2018
- Patient-Centered Outcomes Research Institute Advisory Panel on Clinical Trials, 2014-2016
- University of Alabama, Center for Exercise Medicine External Advisory Committee, 2016
- Program Committee Member, American Institute for Cancer Research 2016 Conference on Nutrition, Physical Activity, Obesity and Cancer
- Consortium Member: NCI Randomized Controlled Trials of Lifestyle Weight Loss Interventions for Genome-Wide Association Studies, 2016-
- AACR Cancer Prevention Committee, 2010-
- World Cancer Research Fund (WCRF) Continuous Update Project Panel, 2010-
- 2008 U.S. Dept. Health and Human Services Physical Activity Guidelines Advisory Committee, 2007- 2008 (Chair, Cancer Working Group)
- Cancer Prevention Research Institute of Texas, Prevention Review Committee, 2009-2015
- Chair, Transdisciplinary Research on Energetics and Cancer (TREC) Steering Committee 2006-7
- Chair, Cancer Interest group, the Obesity Society, 2006-7
- Steering Committee for International Position Paper and Consensus Conference on Women's Health and the Menopause, NHLBI-Lorenzi Foundation sponsors, 1998 – 2002
- International Advisory Board to the 4th International Symposium on Women's Health and Menopause, 2000 – 2001 and 2004
- Professional Advisory Committee, Breastcancer.org, 2003 –
- Women's Health Research Coalition, 2002
- Women's Health Initiative Committee Membership: Morbidity and Mortality (Co-Chair); Performance Monitoring Outcomes Committee (Chair); Coordinating Center Outcomes Scientific Committee (Chair); Coordinating Center Representative to WHI Program Advisory Committee, 1994-1995; Genetics Working Group; Cancer Biomarkers Working Group
- Consultant, *Moving Forward Study*, University of Illinois, Chicago (PI, Melinda Stolley), 2013-
- Consultant, *The Energy Balance and Breast Cancer Aspects studies: EBBA-I and EBBA-II*, Oslo University Hospital, Oslo, Norway (PI, Inger Thune), 2013-
- American Institute of Cancer Research Meeting Program Committee member, 2010, 2016
- Cancer Prevention Expert Panel, Pennington Biomedical Research Center (Baton Rouge, LA), 2010
- External Advisory Committee, Cooper Clinic, Dallas, Tx, April 2006
- Steering Committee, LISA Trial of Weight Loss for Breast Cancer Patients, Novartis Canada 2005 – 2007
- Chair, Breast Clinical Endpoints Committee, DANCE trial of testosterone patch safety, Proctor & Gamble, 2006-7
- External Reviewer for NCI Nutritional Epidemiology Program, 2005, 2013
- Data and Safety Monitoring Board, "Project Alive", Kaiser Oakland (B. Sternfeld, PI)
- Member, NCI Transdisciplinary Research Working Group, co-Chair section on Lifestyle, 2006
- Panels for American Cancer Society Guidelines on *Diet, Nutrition and Cancer Prevention* and Guidelines for Cancer Patients and Survivors (2001, 2003, 2005)
- Working Group for International Agency for Research on Cancer Handbook of Cancer Prevention: Volume 6 – Weight control and physical activity, 2000 – 2001
- Advisory Board for the Tomorrow Study (Alberta, Canada, Cancer Cohort Study), 1999 - 2001
- Advisor to The effects of weight loss and exercise on biomarkers of breast cancer risk- a randomized pilot trial (M. Harvie, A. Howell, Manchester, England)
- Participant, "Workshop on Physical Activity and Breast Cancer", National Action Plan on Breast Cancer, Nov. 1997

- Invitee, “Beyond Hunt Valley: Research on Women’s Health for the 21st Century”, Nov. 1997
- Participant, “Breast Cancer in Minorities”, National Action Plan on Breast Cancer, March 1999
- 2005 ASPO Annual Meeting Program Committee
- Member, Steering Committee for International Position Paper and Consensus Conference on Women’s Health and the Menopause, NHLBI-Lorenzi Foundation sponsors, 1998

Editorial Boards

- Cancer Prevention Research, 2008 - 2014
- Journal of Women’s Health, 1998 –
- Medscape Women's Health and Ob/Gyn & Women's Health, 2001 – 2002

Grant Reviewing

- Chair, Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Prevention, January 2017
- Member, Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Prevention, January 2018
- Florida Department of Health Research Program Peer Review, 2017
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Epidemiology, February, 2016
- NCI Omnibus: Biomarkers R03 & R21 SEP-12 Review Committee 2015
- NCI Omnibus: Cancer Management & Behavior 2014
- MD Anderson NCI CCSG Review 2013
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program Breakthrough Award, Epidemiology/Prevention 2013
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program Training-Epidemiology - Prevention (2 cycles) 2013
- NIH Special Emphasis Panel Member September 2012
- NIH PRDP Study Section Member 2008-2012 (ad hoc 2006-2008)
- Susan G. Komen for the Cure 2009 - 2013
- Cancer Prevention & Research Institute of Texas 2009 – 2015
- Qatar National Priorities Research Program 2010-2013
- Catalan TV3 Marató Call 2005, 2013
- San Diego State/UC San Diego Pilot Grant Reviewer 2012
- FHCRC and UW Pilot Grant Reviews yearly
- NCI Cancer Centers Review Group Ad Hoc Member May 2007
- Pennsylvania Interim Performance Review 2007, 2008, 2010, 2012
- Marsha Rivkin Center for Ovarian Cancer Research Grants 2012
- Memorial Sloan Kettering Cancer Center NCI CCSG Review 2007
- Department of Defense Breast Cancer Program Predoctoral Fellowship Grants, 2006
- Chair, NIH Special Study Section “Mechanisms of Physical Activity Behavior Change” 3/04
- NIH EDC-2 Special Study Section, Sept. 9-10, 1997
- Alberta Cancer Board Grants, 1998-2002 and other Canadian agencies, and for Spanish and Italian Foundations
- NCI Administrative Supplements for Disseminating Evidence-based Research Products 8/04
- Member, ACSM Research Review Committee 2004 – 2006

Journal Reviewing

- JAMA, Archives of Internal Medicine, American Journal of Epidemiology, Journal of the National Cancer Institute, Annals of Internal Medicine, European Journal of Cancer, British Journal of Cancer, Cancer Causes & Control, Cancer Epidemiology Biomarkers & Prevention, Annals of Epidemiology, Epidemiology, and Nutrition

College Fellowship and Membership

- The Obesity Society (Fellow 2003 -)
- American College of Sports Medicine (Fellow 2003 -)
- American College of Epidemiology (Fellow 1999 -)

Professional Licenses and Certification

- Board Certified, American Board of Internal Medicine, 1992
- Physician & Surgeon License, State of Washington, 7/21/91-2/18/18
- DEA License, Expires 2017, Schedules 2, 2N, 3, 3N, 4, 5

LEADERSHIP

- Director, FHCRC Prevention Center, 2002-2012
- Chair, TREC Steering Committee 2006-7
- Chair, Cancer Interest Group, Obesity Society 2007-8
- Chair, Cancer Subcommittee, DHHS Physical Activity Guidelines Advisory Committee 2016-18
- Member, Leadership Group, DHHS Physical Activity Guidelines Advisory Committee 2016-18
- Chair, Cancer Working Group, DHHS Physical Activity Guidelines Advisory Committee 2007-8
- Chair, Section on Mechanisms, IARC Handbook of Cancer Prevention 2002: Physical Activity and Weight Control, 2000-1
- Organized and Chaired Symposium on Physical Activity and Cancer, American College of Sports Medicine, St. Louis, June 2002

REFEREED PUBLICATIONS

(** refers to student papers under my supervision; ^ denotes papers from studies on which I was PI)

1983

1. Shy K, **McTiernan A**, Daling J, and Weiss N: Oral contraceptive use and the occurrence of pituitary prolactinoma. Journal of the American Medical Association 249:2204-2207, 1983.

1984

2. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid carcinoma in women in relation to reproductive and hormonal factors. American Journal of Epidemiology 120:423-435, 1984.
3. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid carcinoma in women in relation to radiation exposure and history of thyroid disease. Journal of the National Cancer Institute 73:575-581, 1984.

1985

4. **McTiernan A**, Chu J, and Thomas D: Cancer in whites in the Pacific Basin. In Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin. National Cancer Institute Monograph 69:65-72, 1985.

1986

5. ^**McTiernan A**, Weiss N, and Daling J: Bias resulting from using the card-back system to contact patients in epidemiologic studies. American Journal of Public Health 76:71-73, 1986.
6. **McTiernan A**, Whitehead A, Thomas D, and Noonan E: Efficient selection of controls for multi-centered collaborative studies of rare diseases. American Journal of Epidemiology 123:901-904, 1986.
7. **McTiernan A**, Thomas D, Johnson L, and Roseman D: Risk factors for estrogen receptor-rich and estrogen receptor-poor breast cancers. Journal of the National Cancer Institute 77:849-854, 1986.
8. **McTiernan A** and Thomas D: Evidence for a protective effect of long-term lactation on risk of breast cancer: results from a case-control study. American Journal of Epidemiology 124:353-358, 1986.
9. ^Mueller B, **McTiernan A**, and Daling J: Level of response in epidemiologic studies using the card-back system to contact patients. American Journal of Public Health 76:1331-1332, 1986.

1987

10. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. Cancer Research 47:292-295, 1987.

1991

11. Rosenblatt KA, Thomas DB, **McTiernan A**, et al: Breast cancer in men: aspects of familial aggregation. Journal of the National Cancer Institute 83:849-54, 1991.
12. Demers PA, Thomas DB, Rosenblatt KA, **McTiernan A**, et al: Occupational exposure to electromagnetic fields and breast cancer in men. American Journal of Epidemiology 134:340-47, 1991.

1992

13. Thomas DB, Jiminez LM, **McTiernan A**, et al: Breast cancer in men: risk factors with hormonal implications. American Journal of Epidemiology 135:734-48, 1992.

1993

14. Stalsberg H, Thomas DB, Rosenblatt KA, Jiminez LM, **McTiernan A**, et al: Histologic types and hormone receptors in breast cancer in men--a population-based study in 282 North American men. Cancer Causes and Control 4:143-51, 1993.

1994

15. Thomas DB, Rosenblatt K, Jiminez LM, **McTiernan A**, et al: Ionizing radiation and breast cancer in men. Cancer Causes and Control 5:9-14, 1994.

1995

16. Bowen D, Green P, Kestin M, **McTiernan A**, Carroll D: Effects of decreasing dietary fat on psychological well-being. Cancer Epidemiology, Biomarkers, and Prevention 4:555-59, 1995.
17. **McTiernan A**, Rossouw J, Manson J, et al: Informed consent in the Women's Health Initiative. Journal of Women's Health 5:519-529, 1995.

1996

18. Prentice R, Rossouw JR, Johnson, SR, Freedman LS, **McTiernan A**. The role of randomized controlled trial in assessing the benefits and risks of long-term hormone replacement therapy: example of the Women's Health Initiative. Menopause, 1996;3:71-76.
19. **McTiernan A**, Stanford JL, Weiss NS, Daling JR, Voigt LF: Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. Epidemiology 1996;7:598-604.

1997

20. Burke W, Peterson G, Lynch P, Botkin J, Daly M, Garber J, Kahn MJE, **McTiernan A**, Offitt K, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 1. Hereditary nonpolyposis colon cancer. JAMA 1997;277:915-919.
21. Burke W, Daly M, Garber J, Botkin J, Kahn MJE, Lynch P, **McTiernan A**, Offitt K, Perlman J, Petersen G, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 2. BRCA1 and BRCA2. JAMA 1997;277:997-1003.
22. **McTiernan A**, Gilligan M, Redmond C: Assessing individual risk for breast cancer: risky business. J Clinical Epidemiology 1997;50:547-556.

1998

23. Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Controlled Clinical Trials 1998;19:61-109.
24. **McTiernan A**, Stanford J, Daling J, Voigt L: Prevalence and correlates of physical activity in women aged 50-64 years. Menopause 1998;5:95-101.
25. ^**McTiernan A**, Kumai C, Bean D, Hastings R, Schwartz R, Ulrich N, Gralow J, Potter J. Anthropometric and hormone effects of an 8-week exercise-diet intervention in breast cancer patients: results of a feasibility pilot study. Cancer Epidemiology Biomarkers Prevention 1998;7:477-81.
26. Hoffman-Goetz L, Apter D, Demark-Wahnefried W, Goran M, **McTiernan A**, Reichman M. Mechanisms for an association between physical activity and breast cancer. Cancer (supplement) 1998;83:621-628.
27. **McTiernan A**, Ulrich N, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Causes and Control 1998;9(5)487-509.

1999

28. Cheblowski RT, **McTiernan A**. Elements of informed consent for Hormone Replacement Therapy in patients with diagnosed breast cancer. Journal of Clinical Oncology 1999;17(1):130-42.
29. ^Negri E, Ron E, Franceschi S, DalMaso L, Mark SD, Preston-Martin S, **McTiernan A**, et al. A pooled analysis of thyroid cancer case-control studies: Methods. Cancer Causes and Controls 1999;10:131-142.
30. ^Negri E, DalMaso L, Ron E, LaVecchia C, Mark SD, Preston-Martin S, **McTiernan A**, et al. Menstrual and reproductive factors and thyroid cancer. Cancer Causes and Controls 1999;10:143-155.
31. ^LaVecchia C, Ron E, Franceschi S, DalMaso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, **McTiernan A**. Oral contraceptives, menopausal replacement treatment and other female hormones and thyroid cancer. Cancer Causes and Controls 1999;10:157-166.
32. Durfy S, Bowen D, Burke W, **McTiernan A**, et al. Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in Western Washington. Cancer Epidemiology Biomarkers and Prevention 1999;8:369-376.
33. ^**McTiernan A**, Ulrich CM, Yancey D, Slate S, Nakamura H, Oestreicher N, Bowen D, Yasui Y, Potter J, and Schwartz R. The Physical Activity for Total Health (PATH) Study: rationale and design. Medicine and Science in Sports and Exercise 1999;31:1307-1312.
34. **McTiernan A**, Potter J, Bowen D, Schwartz R. Exercise clinical trials in cancer prevention research: a call to action. Cancer Epidemiology Biomarkers and Prevention 1999; 8:201-207.
35. Bowen D, **McTiernan A**, Burke W, Powers D, Pruski J, Durfy S, Gralow J, Malone K. Participation in breast cancer risk counseling among women with a family history. Cancer Epidemiology Biomarkers and Prevention 1999; 8:581-586.
36. Rosenblatt KA, Thomas DB, Jimenez LM, Fish B, **McTiernan A**, et al. Diet and breast cancer in men. Cancer Causes and Control 1999;10:107-113.
37. ^Franceschi S, Preston-Martin S, DalMaso L, Negri E, LaVecchia C, **McTiernan A**, et al. A pooled analysis of thyroid cancer case-control studies. IV. Benign thyroid diseases. Cancer Causes and Control 1999;10:583-595.
38. ^LaVecchia C, Ron E, Franceschi S, DalMaso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, **McTiernan A**. A pooled analysis of thyroid cancer studies. Anthropometric factors. Cancer Causes and Control 1999;10:583-595.

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39. Burke W, Culver JB, Bowen D, Lowry D, Durfy S, **McTiernan A**, Anderson, MR. Genetic counseling for women with an intermediate family history of breast cancer. American Journal of Medical Genetics 2000;90(5):361-8.
40. **McTiernan A**. The associations of energy balance and body mass index with breast cancer risk in United States women from diverse racial and ethnic backgrounds. Cancer 2000;88:1248-1255.
41. Bowen DJ, **McTiernan A**, , Rosenberg E, Powers P, Feng Z: Recruiting women into a smoking cessation program to control weight: who might quit? Women and Health 2000;31(4):41-58.
42. Wingo PA, Calle EE, **McTiernan A**. How does breast cancer mortality compare with other cancers and cardiovascular disease at different ages in U.S. women? Journal of Women's Health 2000;9:999-1006.
43. **McTiernan A**. Physical Activity and the Prevention of Breast Cancer. Medscape. Invited as Expert Opinion. October 2000; 5(5). Available at <http://www.medscape.com/Medscape/WomensHealth/journal/2000/v05.n05/wh7419.mcti/wh7419.mcti-01.html>

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45. Davidoff R, **McTiernan A**, Constantine G, Davis KD, Balady GJ, Mendes LA, Rudolph RE, Bowen, DJ. Echocardiographic evaluation of women previously treated with fenfluramine: Long-term follow-up of a randomized, double-blind, placebo-controlled trial. Archives of Internal Medicine. 2001;161:1429-1436.
46. Marrett L, Theis B, Ashbury FD, and an Expert Panel. Workshop report: physical activity and cancer prevention. (member of the expert panel). Chronic Diseases in Canada 2001;21:143-149.
47. La Vecchia C, Brinton L, **McTiernan A**. Menopause, hormone replacement therapy and cancer. Maturitas 2001; 39: 97-115.
48. **McTiernan A**, Burke W, Bars J, et al. Comparison of two breast cancer risk estimates in women with a family history of breast cancer. Cancer Epidemiology Biomarkers and Prevention 2001;10: 333-338.

49. ^Bosetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, Galanti MR, Mark SD, Preston-Martin S, **McTiernan A**, Land C, Mabuchi K, Jin F, Wingren G, Hallquist H, Glatte E, Lund E, Levi F, Linos D, La Vecchia C. A pooled analysis of case-control studies of thyroid cancer: fish and shellfish consumption. Cancer Causes and Control 2001;12:375-382.
 50. Shors AR, Solomon C, **McTiernan A**, White E. Melanoma risk in relation to height, weight, and exercise (United States) Cancer Causes and Control 2001; 12(7):599-606. Cancer Causes Control. 2001 Sep;12(7):599-606.
 51. Tavani A, La Vecchia C, Brinton LA, **McTiernan A**. Hormone replacement therapy and risk of endometrial cancer. Tumori. 2001 Sep-Oct;87(5):S20-1.
 52. LaVecchia C, Brinton LA, **McTiernan A**. Hormone replacement therapy and breast cancer risk: epidemiology. Journal fur Menopause 2001;8:5-7.
 53. Friedenreich C, Marrett LD, Members of the Canadian Breast Cancer Initiative Working Group on Primary Prevention of Breast Cancer and an Expert Panel. Workshop report: identification of research needs in breast cancer etiology. Chronic Diseases in Canada 2001;22:41-49 (member of the Expert Panel).
- 2002**
54. ^**Irwin ML, **McTiernan A**. Exercise effect on body weight in postmenopausal women: the Physical Activity for Total Health Study. In RA Lobo, PG Crosignani, R Paoletti, F Bruschi (eds). Women's Health and Menopause: New Strategies – Improved Quality of Life. Dordrecht, Kluwer Academic Pub. 2002, pp. 345-352.
 55. Chlebowski RT, Aiello E, **McTiernan A**. Weight loss in breast cancer patient management. J. Clinical Oncology 2002;20(4):1128-1143.
 56. ^**Slate S, Yasui Y, Ulrich C, **McTiernan A**. Mailing strategies and recruitment into an intervention trial of the exercise effect on breast cancer biomarkers. Cancer Epidemiology Biomarkers and Prevention 2002; 11: 73-77.
 57. Hendrix S, Clark A, Nygaard I, Aragaki A, Barnabei V, **McTiernan A**. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J. Obstet Gynecol 2002 Jun;186(6):1160-6.
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68. Bowen D, Powers D, Anderson R, Burke W, **McTiernan A**, Durfy S, Helmes A. Predicting breast cancer screening with emotion and cognition. Journal of Social and Clinical Psychology 2003;22(2):213-232.
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76. ^{***}Tworoger S, Yasui Y, Ulrich CM, Vitiello M, Bowen D, Irwin M, Aiello EJ, Schwartz RS, Potter J, **McTiernan A**. Effect of a yearlong moderate to vigorous intensity exercise or low intensity stretching intervention on self-reported sleep quality measures in postmenopausal women. Sleep 2003;26(7): 830-6.
77. **McTiernan A**. Behavioral risk factors in breast cancer: can risk be modified? The Oncologist. 2003;8(4):326-34.
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83. ^{***}Tworoger SS, Chubak J, Aiello EJ, Ulrich CM, Atkinson C, Potter JD, Yasui Y, Stapleton PL, Lampe JW, Farin FM, Stanczyk FZ, **McTiernan A**. Association of *CYP17*, *CYP19*, *CYP11B1*, and *COMT* polymorphisms with serum

- and urinary sex hormone concentrations in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2004 13: 94-101.
84. **McTiernan A.** Physical activity after cancer: physiologic outcomes. Cancer Investigation 2004;22:68-81.
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 90. Tworoger SS, Davis S, Mirick D, Emerson S, Lentz M, **McTiernan A** The effect of a nighttime magnetic field exposure on sleep patterns in young women. Am. J. Epidemiology 2004;160(3):224-9.
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2. **McTiernan A,** Gralow J, Talbott L. *Breast Fitness: An Optimal Exercise and Health Plan for Reducing Your Risk of Breast Cancer*. St. Martin's Press, New York. October 2000 (hardcover), October 2001 (softcover)
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5. **McTiernan A.** (Editor) Physical Activity, Dietary Calorie Restriction, and Cancer (Energy Balance and Cancer). Springer; 1st Edition. November 19, 2010.

REPORTS, EDITORIALS, BOOK CHAPTERS, LETTERS, AND INVITED REVIEWS

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9. **McTiernan A.** Recent Controversies in Mammography Screening for Breast Cancer. *Medscape Women's Health eJournal* 2002;7(2).
10. Chlebowski R, **McTiernan A.** Biological significance of interventions that change breast density. *J Natl Cancer Inst.* 2003 Jan 1;95(1):4-5.
11. **McTiernan A.** Lifestyle Factors in Breast Cancer. *Breast Cancer Online*. 2003
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13. **McTiernan A.** Obesity and Cancer: Potential Management Strategies. *American Society for Clinical Oncology Proceedings*. 2004.
14. **McTiernan A.** Obesity in the Breast Cancer Survivor. In *Nutritional Oncology*. Heber D. and Blackburn G. (Eds). San Diego, Academic Press, 2005.
15. **McTiernan A.** Low carb diets: will they be effective in reducing breast cancer risk? *American Society for Clinical Oncology Proceedings*, 2005.
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24. **McTiernan A.** Physical Activity, Weight, Diet and Breast Cancer Risk Reduction. Invited Commentary on Eliassen et al. Physical activity and risk of breast cancer among postmenopausal women. *Arch Int Med* 2010 Nov 8;170(20):1792-3
25. Chan D, Thune I, **McTiernan A.** Invited commentary on Chan et al., Body Mass Index and Survival in Women With Breast Cancer–Systematic Literature Review and Meta-Analysis of 82 Follow-Up Studies. *Practice Update*. <http://www.practiceupdate.com/explore/> May, 2014.
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27. Duggan C, Gross MD, **McTiernan A.** Diet and Exercise and Serum Markers of Oxidative Stress-Response. *Cancer Prev Res (Phila)*. 2017 Aug;10(8):487.

MANUSCRIPTS SUBMITTED FOR PUBLICATION

1. Frydenberg H, Ursin G, Iversen A, Fagerland MW, Ellison PT, Wist EA, Egeland T, Wilsgaard T, **McTiernan A**, Furberg A-S, Thune I. High-density lipoprotein-cholesterol (HDL-C), daily estradiol and progesterone and mammographic density in premenopausal women. Submitted to The Breast 2015
2. Lofterød T, Frydenberg H, Eggen AE, **McTiernan A**, Mortensen ES, Wist EA, Akslen LA, Reitan JB, Wilsgaard T, Thune I. Triglycerides and weight change throughout life influence breast cancer development. The EBBA Life study. Submitted to Cancer Causes & Control 2016.
3. Mason C, deDieu Tapsoba J, Duggan C, Wang CY, Alfano CM, **McTiernan A**. Disordered eating behaviors and weight loss outcomes in a 12-month randomized trial of diet and/or exercise intervention in postmenopausal women. Submitted to American Journal of Clinical Nutrition 2018.
4. Chan DS, Abar L, Cariolou M, Nanu N, Greenwood DC, Bandura EV, **McTiernan A**, Norat T. World Cancer Research Fund International – Continuous Update Project: systematic literature review and meta-analysis of cohort studies on physical activity, adiposity, and weight change and breast cancer risk. Submitted to British Medical Journal. 2018

INVITED SCIENTIFIC PRESENTATIONS (does not include conference abstracts)

1. "Women's Health and the Women's Health Initiative." Fred Hutchinson Cancer Research Center, WHI Clinical Center Staff Trainings, 1993-1997.
2. "The Women's Health Initiative: An Overview." University of Washington, Department of Epidemiology Seminars, February 8, 1994.
3. "Risk Assessment for Breast Cancer." University of Washington, Department of Surgery Breast Cancer Conference, April 26, 1994.
4. "Risk Assessment for Breast Cancer." Breast Cancer in Young Women, University of Washington Continuing Education Conference, August 6, 1994.
5. "Assessing Individual Risk for Breast Cancer." Cancer in Lesbians Symposium, Fred Hutchinson Cancer Research Center, December 2, 1994.
6. "Breast Cancer in High Risk Populations: Women's Health Initiative." Fred Hutchinson Cancer Research Center Scientific Retreat, December 7, 1994.
7. "The Women's Health Initiative." Invited presentation at American Society for Preventive Oncology, Women's Cancers Study Group Meeting, March 11, 1995.
8. "Prevention in Practice and Trials." Current Concepts in the Early Detection of Breast Cancer, Multicare, Madigan Army Medical Center, and American Cancer Society 3rd Annual Oncology Conference, April 11, 1995.
9. "Exercise and Breast Cancer." Beating Breast Cancer in the '90's: What Everyone Needs to Know about Breast Cancer, University of Washington/Fred Hutchinson Cancer Research Center, April 23, 1996.
10. "Women's Health Initiative." Women's Health Grand Rounds, University of Washington Medical Center-Roosevelt, January 6, 1996.
11. "Exercise and Cancer." Interdisciplinary Cancer Course, Fred Hutchinson Cancer Research Center, March 26, 1997.
12. "Exercise and Breast Cancer." Nutrition Seminar, Department of Nutrition, University of Washington School of Public Health, April 10, 1997.
13. Panel Discussant, "Epidemiologic Issues", NAPBC Workshop on Physical Activity and Breast Cancer, Nov 13-14, 1997.
14. "Diet and Exercise" Breast Cancer Forum: Clinical Implications of Current Research, FHCRC, October 7, 1998.
15. "Exercise and Breast Cancer" American College of Sports Medicine, Seattle, WA, June 2, 1999.
16. "Physical Activity and Reproductive Hormones" Cooper Institute Conference on Physical Activity and Cancer, Dallas, Texas, November 5-7, 2000
17. "Weight Matters in Breast Cancer Prevention and Rehabilitation" Oncology Grand Rounds. Southwest Cancer Center at University Medical Center, Lubbock, Texas, March 2001
18. "Body mass, physical activity, and sex hormones in postmenopausal breast cancer patients". American Cancer Society Science Writers Conference, April 2001

19. "Obesity and Women's Cancer" Keynote Lecture, North American Association for the Study of Obesity, October 2001.
20. "Physical Activity and Breast Cancer", Women's Sports International, St. Louis, June 2002.
21. "Exercise and Breast Cancer", FHCRC Oncology Grand Rounds, October 2002.
22. "Physical Activity after Cancer: Physiologic Outcomes" in Exercise and the Cancer Survivor: What Should we Recommend?, American Dietetic Association Food and Nutrition Conference and Exhibition, Philadelphia, October 2002.
23. ** "Exercise and the Prevention of Colorectal Cancer" European School of Oncology Second Colorectal Cancer Conference, Rome, Italy, October 2002.
24. "Energy Balance – an Etiologic Factor in Human Cancer: Randomized Trial of Exercise Effect on Breast Cancer Biomarkers." Oslo Norway, July 2002.
25. "Exercise and Breast Cancer: Impact on Prevention and Recurrence" The Gibson Lecture in Cancer Prevention Endowed Lectureship, University of Virginia School of Medicine, February 26, 2003
26. "Exercise, Body Fat, and Breast Cancer" Florence Ettelson Memorial Lectureship Medicine Grand Rounds, Providence St. Vincent Medical Center, Portland, OR October 2003
27. "Exercise and Breast Cancer" U. Washington Geriatrics Grand Rounds October 2003
28. "Body Mass Index & Breast Cancer Risk" Challenges & Controversies in Breast Cancer, U Washington School of Medicine CME, October 2003
29. "Diet and Physical Activity" 2nd Emerging Trends in Adjuvant Therapy of Breast Cancer Conference, New York City, October 2003.
30. "Exercise in the Prevention of Breast and Colon Cancer" New England American College of Sports Medicine, November, 2003.
31. "Managing Toxicities of Therapy: Weight Loss and Exercise" School of Breast Oncology, November 2003
32. "Exercise and Breast Cancer Prevention" U. Hawaii, January 2004
33. ** "Obesity and Cancer" 2nd International Conference on the Future of Supportive Therapy in Oncology, St. Kitts, Carribean, February 2004
34. "Exercise and Breast Cancer" University of Alabama at Birmingham, CNRC/Nutrition Sciences Seminar Series, March 2004
35. "WHI Estrogen plus Progestin and Breast Cancer Results" FHCRC Gynecologic Cancer Research Program, March 2004
36. ** "Exercise Effects on Total Body Fat, Intra-Abdominal Fat, Insulin, Leptin, and the Metabolic Syndrome in Menopause" Plenary Session, 5th International Symposium on Women's Health and Menopause, Florence, Italy, April 2005
37. "Exercise and Women's Health" University of Virginia, May 2004
38. "Colon ca, biomarkers, and exercise" American College of Sports Medicine, 2004
39. "Obesity Management in Cancer Patients" ASCO, June 2004
40. ** "Effect of Physical Activity on Breast and Colon Cancer Biomarkers" Ireland/Northern Ireland/NCI Cancer Consortium Seminar on Obesity and Cancer, Dublin, Ireland, September 2004
41. "Exercise Trials in Cancer Prevention" AACR Frontiers in Cancer Prevention, Seattle, WA October 2004
42. "Physical Activity, Endogenous Hormones, and Cancer Etiology" Plenary Session AACR Frontiers in Cancer Prevention, Seattle, WA October 2004
43. "Obesity in Breast Cancer Patients" School of Breast Oncology, Atlanta, Georgia, November 2004
44. "Nutrition, Physical Fitness, and Cancer" Aultman Cancer Center, Canton, Ohio, November 2004
45. "Effects of Menopausal Hormone Therapy and Tamoxifen on Mammographic Density" University of Virginia, Department of Radiology, February 2005.
46. "Optimizing Health Outcomes" in Oncology Care in the 21st Century: Integrating Care along the Health Care Continuum, Arthur G. James Cancer Hospital Ohio State University, February 2005
47. "Obesity, Exercise, and Breast Cancer", Tyler, Texas Breast Cancer Conference (talks to oncologists and lay audiences) March 2005
48. "Breast Fitness" talk to women's health providers, Anchorage, Alaska, May 2005
49. "Low Carb Diets: Will They Be Effective in Reducing Breast Cancer Risk?" ASCO, Orlando 2005.
50. ** "Biologic mechanisms involved in the association between physical activity and cancer: results from recent

- randomized controlled intervention trials” Eurocancer, Paris, June 2005.
51. ** “Exploring Mechanisms Relating Energy Balance and Cancer” IARC, Lyon, France, June 2005.
 52. “Prevention of New and Recurrent Cancers: Lifestyle and Chemoprevention” and “Cancer Screening and Management: The PCP's Role” Issues in Aging Conference, New Orleans, July 2005
 53. "Exercise and Cancer Prevention" Rockefeller, NYC, September 2005
 54. ** “Open Forum of Breast Health”, Mexico City, Mexico, October 2005
 55. “Breast Fitness: Exercise for Breast Cancer Patients and Survivors”, Cancer Wellness Center Northbrook, IL, November 2005
 56. “Obesity in Breast Cancer Patients”, School of Breast Oncology, Atlanta GA, November 2005
 57. "Insulin Resistance Syndrome and Cancer Risk", International Conference on Metabolic Syndrome, San Francisco, November 2005
 58. “Selected Major Findings from the OS Results: Breast Cancer”, WHI Conference, Bethesda, February 2006.
 59. “Intermediate Endpoints in Energy Balance and Physical Activity Trials” NCI Workshop on State of the Evidence for a Weight Control Trial to Prevent Breast Cancer, Bethesda, March 2006.
 60. “Physical Activity and Cancer Recurrence and Survival”, Symposium: "Physical Activity across the Cancer Continuum" for the CDC International Congress on Physical Activity and Public Health, Atlanta, April 2006
 61. “Exercise, Estrogens, and Breast Cancer: Physical Activity Trials” American College of Sports Medicine, May 2006.
 62. “Exercise and Nutrition in Chemoprevention” WCRF/AICR International Research Conference, Washington DC, July 2006.
 63. ** “Exercise and Cancer Prevention”. National University of Singapore, Singapore, July 2006.
 64. ** “Breast Cancer Prevention”, “Lifestyle, Diet, and Breast Cancer”, “Lifestyle changes may reduce the risk of recurrence” Mexican Association of Breast Diseases 5th Annual Meeting, Leon, Mexico, August 2006.
 65. “WHI and Breast Cancer” Seattle Gynecological Society, Seattle, September, 2006
 66. "Physical Activity, Weight Control, and Cancer Prevention” Dana Farber Cancer Center Channing Laboratory and Harvard School of Public Health Seminar Series Speaker, October 2006.
 67. “Obesity in Breast Cancer Patients”, School of Breast Oncology, Atlanta GA, November 2006
 68. “Energy Balance and Cancer: Human Intervention Studies” NCI Energy Balance Working Group, Bethesda, MD, January 2007
 69. “Overweight, Obesity, and Sedentary Lifestyle in Breast Cancer Prognosis”. Interdisciplinary Science, Health Promotion, and Disease Prevention. Pasadena, CA. May 2, 2007.
 70. “Transdisciplinary Research to Elucidate the Pathways Linking Components of Energy Balance to the Cancer Process” Transatlantic Research and Innovation Symposium. Research Triangle Park, North Carolina, May 3, 2007.
 71. “Obesity, Physical Activity, & Breast Cancer” University of Washington CNRU May 11, 2007
 72. “Women’s Health Initiative Clinical Trials” Northwestern University Clinical Research Educational Conference, Chicago, May 18, 2007.
 73. “Exercise and Weight Loss in Women and Men” Northwestern University Dept of Preventive Medicine, May 18, 2007.
 74. FASEB Energy Balance, Body Fat & Disease, “Exercise and Cancer Prevention”, and chair of session “Exercise and Cancer Prevention & Prognosis” Indian Wells, CA, August 2007
 75. MD Anderson Cancer Prevention Grand Rounds, “Overweight, Obesity, Physical Activity, and Breast Cancer Prevention” Houston, Sept 2007
 76. MD Anderson Integrative Medicine Program Lecture Series talk “Obesity, Weight Loss, and Physical Activity for Cancer Patients and Survivors” Houston, Sept 2007
 77. **Breast Health Global Initiative “Primary prevention of breast cancer: lifestyle changes, diet, western lifestyle”, Budapest, Hungary, October 2007
 78. “Obesity in Breast Cancer Patients”, School of Breast Oncology, Atlanta GA, November 2007
 79. “Breast Cancer: Women at Risk and New Strategies for Prevention”, Practicing Clinicians Exchange, San Francisco, CA November 2007
 80. “Exercise Effect on Inflammation and Other Cancer Biomarkers”, Southeast ACSM, Birmingham, AL, February 2008
 81. “Professional Development for Women”, Southeast ACSM, Birmingham, AL, February 2008
 82. “Exercise and Body Composition Change Effects on Sex Hormones in Postmenopausal Women”, AACR – TREC

Markers & Mediators, Virginia, February 2008

83. "Obesity in Breast Cancer Risk and Prognosis", Case Western University, Cleveland, OH, March 2008
84. "Exercise Interventions in Breast Cancer Prevention and Outcomes", Cleveland, OH, March 2008
85. "TREC Talk", Cancer Prevention and Research Center Retreat, Coeur d' Alene, ID, March 2008
86. ** "Fitness vs. Fatness: Evidence from Epidemiologic and Intervention Studies on the Separate and Combined Effects of Physical Activity and Obesity on Cancer Risk", International Physical Activity Meeting, Amsterdam, April 2008
87. "Influence of Exercise on Immune Function: Possible Link to Breast Cancer", ACSM, Indianapolis, May 2008
88. "Breast Cancer Prevention and Survivorship through Lifestyle and Chemoprevention", Memorial Sloan Kettering Cancer Center, New York City, NY, September 2008
89. ** "Early Detection, Diet, Physical Activity, and Cancer", Women in High Places meeting, Riyadh, Saudia Arabia, October 2008
90. ***"Diet and Breast Cancer", Saudi Arabian Cancer Conference, Riyadh, Saudia Arabia, October 2008
91. "Physical Activity & Weight Control in Breast Cancer Prevention & Prognosis", Alaska Conference: "Reducing the Risk, Advancing the Cure: New Recommendations, New Options for Primary Care Providers and Survivors." Televised from Seattle, October 2008
92. "Lessons Learned from Real-Life Lifestyle Interventions", The Obesity Society, Phoenix, AZ, October 2008
93. "Breast Cancer: Weight Loss and Exercise", School of Breast Oncology, Atlanta, GA, November 2008
94. "Fitness vs. Fatness in Breast Cancer Risk and Prognosis", Frontiers of Cancer Prevention, Washington, DC, November 2008
95. "Effects of Exercise and Obesity on Inflammation and Cancer Risk", University of Washington, DERC Seminar Series, February 2009
96. "Does Weight Loss Reduce Cancer Risk?" The Obesity Society, October 2009.
97. Roger E. Moe Award for Translational Research Lecture "Effects of Weight and Physical Activity on Breast Cancer Prognosis" University of Washington *Current Concepts and Challenges in Breast Cancer* October 2009
98. "Lessons learned from physical activity (exercise) interventions" AICR Annual Research Conference on Food, Nutrition, Physical Activity and Cancer, Washington, DC, November 2010
99. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2010
100. "Transdisciplinary studies of weight loss and exercise interventions in women at increased risk for breast cancer", AACR, Washington, DC, April 2010
101. "Exercise Effects on Breast Cancer Biomarkers", International Society for Behavioral Nutrition & Physical Activity, Minneapolis, MN, June 2010
102. ***"Physical Activity & Cancer" Lecture, Helsedirektoratet (Directory of Health), Oslo, Norway, December 2010
103. "Physical Activity, Weight Control and Cancer Prevention" Physical Activity and Nutrition seminar series University of Michigan. The School of Kinesiology, February 2011.
104. "Physical Activity in Cancer Prevention" American College of Sports Medicine President's Talk, Denver, CO, June 2011
105. "Breast Cancer Prevention" Foundation for Care Management, Lakewood, WA, January 2011
106. "Breast Cancer Prevention" Foundation for Care Management, Coupeville, WA, February 2011
107. "Inflammation, Insulin, & Obesity in Breast Cancer Survival", University of Texas Southwestern Medical Center, Dallas, Texas, September 2011
108. "Interventions in cancer survivors; issues and challenges in this population", Institute of Medicine Workshop "The Role of Obesity in Cancer Survival and Recurrence", Washington, DC, October 31-November 1, 2011
109. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2011
110. ***"Obesity, Physical Activity, & Related Mechanisms in Breast Cancer Survival", Norwegian Congress in Oncology, Oslo, Norway, November 2011
111. "Impact of Obesity on Cancer " Swedish Hospital Medical Center CME, Seattle, WA May 2012
112. "Effects of Weight Loss and Physical Activity on Cancer Risk Factors: Evidence from Randomized Trials", University of Hawaii, July 2012
113. "The Impact of Intentional Weight Loss on Cancer Risk", The Obesity Society, San Antonio, Texas, September 2012
114. "Dietary Weight Loss and Exercise Effects on Metabolic Hormones in Postmenopausal Women", Fred

- Hutchinson Cancer Research Center Symposium on Metabolism and Cancer, September 2012
115. ***"Lifestyle Modifications to Reduce Cancer Risk and Improve Overall Health", Global Summit on International Breast Health, Vienna, Austria, October 2012
 116. ***" Medical Perspective on the Influential Role of Obesity in the Risk and Prognosis of Breast Cancer" and "Obesity, chronic diseases and cancer, a common link with lifestyle" Mexican Association of Mastology, Villahermosa, Tabasco, Mexico, October 2012
 117. "Effects of Weight Loss and Physical Activity on Cancer Risk Factors: Evidence from Randomized Trials" Oregon Health Sciences University, October 2012
 118. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2012
 119. "Dietary weight loss and exercise effects on metabolic and sex hormones in postmenopausal women." American Association for Cancer Research, Washington, DC, April 2013
 120. "Obesity, Weight Loss, Vitamin D, and Cancer Biomarkers" Fred Hutchinson Cancer Research Center Joint Cancer Prevention/Epidemiology Seminar Series, May 2013
 121. ***"The WCRF/AICR Continuous Update Project – Systematic Reviews on Nutrition, Physical Activity & Health Outcomes in Cancer Survivors" International Union of Nutrition Scientists (IUNS) 20th International Congress of Nutrition, Granada, Spain, 2013
 122. ***"Appraisal of Evidence for Obesity Effects on Cancer" IASO/WCRF Obesity, Physical Activity and Cancer, London, 2013
 123. "Weight Loss & Exercise Effects on Breast Cancer Biomarkers" University of Illinois Symposium, Chicago, October 2013
 124. ***"Obesity, Physical Activity and Cancer" State Institute of Diabetes and Endocrinology & Catholic University Post Graduation course on Endocrinology and Metabolism. Rio de Janeiro, Brazil, October 2013
 125. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2013
 126. "Obesity, Physical Activity and Cancer" Keynote Speaker, The Center for Energy Balance in Cancer Prevention & Survivorship Research Retreat, MD Anderson Cancer Center, February 2014
 127. ***"Exercise in Cancer Prevention & Survivorship", Athens Institute for Education and Research, 10th Annual International Conference on Kinesiology and Exercise Sciences, Athens, Greece, August 2014
 128. ***"Weight Loss & Exercise Effects on Cancer Biomarkers," University of Tromso, Norway, September 2014
 129. "Breast Cancer Survivors: Findings from the Continuous Update Project," American Institute for Cancer Research Annual Conference, October, 2014.
 130. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2014
 131. "Obesity, Weight Loss, & Breast Cancer," University of Iowa Diabetes and Obesity Talks Seminar Series, November, 2014
 132. "Weight Loss & Exercise Effects on Breast Cancer Biomarkers," Memorial Sloan Kettering Cancer Center, New York, February, 2015.
 133. "Physical Activity & Weight Loss Effects on Cancer Biomarkers", NCI Schatzkin Talk, May 2015
 134. "Obesity, Weight Loss, Exercise & Breast Cancer" Seattle Cancer Care Alliance, May 2015
 135. ***"Associations of Weight, Physical Activity, & Diet with Breast Cancer Survival", International Society for Behavioral Nutrition & Physical Activity, Edinburg Scotland, June 2015
 136. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2015
 137. ***"The role of physical activity on cancer risk: epidemiology & molecular mechanisms" WCRF International and World Obesity Federation Joint Conference, September 2016
 138. ***"Anthropometry: What Can We Measure & What Does It Mean?" WCRF International and World Obesity Federation Joint Conference, September 2016
 139. ""Exercise, Weight, and Cancer Risk" University of Alabama Center for Exercise Medicine, Birmingham, September 2016
 140. ***"Long-term Effects of Exercise & Weight on Breast Cancer Biomarkers" University of Tromso, Norway, October 2016
 141. "Exercise, Weight, and Cancer Risk" Roswell Park Prevention Grand Rounds, Buffalo, NY, October 2016
 142. "Modifiable Health Behaviors for Cancer Survivors // Health Promotion: Exercise, Physical Rehab" SCCA Cancer Survivorship for Physicians CME, October 2016
 143. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2016

144. “Physical Activity & Cancer – What We Know, What We Don’t Know” American Institute for Cancer Research AICR’s 25th Research Conference, November 2016
145. ***“Screening for Breast Cancer: Pro”, EuroMedLab, Athens, Greece, June 2017
146. ***“Weight Control and Exercise for Breast Cancer Pts & Survivors”, Mexican Association of Mastology, 14th National Congress, Guadalajara – México, August, 2017
147. “Weight Loss and Exercise” School of Breast Oncology, Atlanta GA, November 2017
148. ***“Effects of Weight Loss on Cancer Biomarkers,” Canadian Cancer Research Conference, Vancouver, BC, Canada, November 2017
149. “Physical Activity and Diet for Cancer Prevention and Treatment: State of the Evidence,” Arizona State University, Tempe, Arizona, February, 2018
150. “Physical Activity for Cancer Prevention and Treatment: State of the Evidence,” Wolffe Lecture, American College of Sports Medicine, May 2018
151. ** Diet, Weight & Exercise in Cancer Prevention & Survival: the World Cancer Research Fund Report,” Oncology Grand Rounds, BC Cancer, Vancouver, BC, Canada, September 2018
152. ***“Physical Activity and Cancer Prevention,” National Center for Sport and Exercise Medicine, University of Loughborough, England, July 2018
153. “Weight Control and Exercise for Breast Cancer Prevention,” National Cancer Institute, Stars in Nutrition and Cancer lecture, October, 2018

** International Presentations

FUNDED RESEARCH PROJECTS (total dollars unless otherwise noted)

Completed

- A Case-Control Study of Thyroid Cancer in Women, **PI: Anne McTiernan**, American Cancer Society Institutional Grant 1N-26-U, 1979-1982.
- Counseling Strategies for Breast Cancer Risk, PI: Deborah Bowen, PhD, NIH Grant #HG/CA01190-01, 1994-97, \$654,409.00.
- Fenfluramine as an Adjunct to Smoking Cessation Therapy, PI: Deborah Bowen, PhD, NIH Grant #R29CA50858, 1990-94.
- Feasibility Study of an Exercise-Diet Program for Breast Cancer Patients, PI: Anne McTiernan, FHCRC Bid and Proposal funds, 1995-1996, \$10,000 (direct)
- Echocardiographic Follow-up to a Randomized Trial of Fenfluramine in Women Smokers, PI: Deborah Bowen, PhD, Wyeth Ayerst research contract, 1998, \$1,957,627.
- A Randomized Controlled Trial of Fat Reduction and Risk of Proliferative Forms of Benign Breast Disease, WHI Ancillary Study, PI: Tom Rohan, MD; **PI of FHCRC subcontract to U. Toronto: Anne McTiernan**, \$13,699.
- Effect of Exercise on Mammogram Densities, **PI: Anne McTiernan**, FHCRC Bid and Proposal funds, 1999-2000.
- SEER Special Studies RFP Interaction of Genetic Susceptibility and Hormonal Exposures in Breast Cancer Prognosis, **PI: Anne McTiernan**, 1999-2001, \$137,465.
- SEER Special Studies RFP Mammographic Breast Density and Breast Cancer Prognosis, **PI: Anne McTiernan**, 1999-2001, \$123,558.
- Genetic Risk Information for a Defined Populations, PI: Deborah Bowen, PhD, NIH grant #HG/CA1190-01, 1998-2001, \$1,143,890.
- Effect of Hormone Replacement Therapy on Mammographic Density, WHI Ancillary Study, PI: Barbara Hulka, MD, MPH; **PI of FHCRC subcontract to UNC Chapel Hill: Anne McTiernan**, 1998-2003, \$876,824.
- Effect of Exercise on Sex Hormones in Postmenopausal Women, **PI: Anne McTiernan**, NIH R01CA/AG69334-01A2, 1997-2003, \$1,562,811.
- Effect of Exercise on Immune Function in Postmenopausal Women: Supplement to Effect of Exercise on Sex Hormones in Postmenopausal Women, **PI: Anne McTiernan**, NIH R01CA/AG69334-01A2, 1998-2003, \$439,112.
- Women’s Intervention Nutrition Study (WINS) FHCRC Clinical Center, PI: Alan Kristal; Past-PI, \$28,400.
- Exercise Intervention Trial for Colorectal Polyp Patients, **PI: Anne McTiernan**, R01 CA77572-01, 2000-2007, \$4,046,212.

- Clinical Coordinating Center, Women's Health Initiative Trial & Observational Study, PI: Ross Prentice; **Role on project: Co-Investigator**, NIH N01-WH-2-2110, 1992-2007+, \$112,336,577.
- Randomized, Double-Blind, Placebo Controlled Trial of 4-OH Tamoxifen Gel in Premenopausal Women with 50-80% Density in Breast tissue Based on Digitized Analysis of Screening Mammography, Besins International U.S. Inc. **PI: Anne McTiernan**, 2002-2003, \$116,165.
- Seattle Cancer & Aging Program – Pilot: Effect of Exercise on Prostate Cancer Biomarkers: An Ancillary Study to a Randomized Controlled Clinical Trial, PI: Peter Rabinovitch; **PI of Pilot Study: Anne McTiernan**, P20 CA103728, 2004-2006, \$39,049.
- Study of Tamoxifen vs. Raloxifene (STAR), PI: R. Clarfeld; **Role on project: Co-Principal Investigator**.
- Exercise and Fitness in Childhood Cancer Survivors, PI: Debra Friedman; **PI of FHCRC Subcontract: Anne McTiernan**, NCI R21, 2004-2006, \$23,904 (direct).
- Proteomic Markers of Health Behaviors, PI: Paul Lampe/Yutaka Yasui; **Role on project: Co-Investigator**, NCI-5 R03 CA108339-02, 2004-2006, \$173,000.
- Randomized placebo-controlled biomarker modulation trial using Celecoxib in premenopausal women at high risk for breast cancer, SWOG, PI: Powell Brown; **PI of FHCRC subcontract: Anne McTiernan**, NIH/NCI CA37429, 2005-2006, \$37,799.
- Effects of Aspirin on Biomarkers of Breast Cancer Risk (Avon Progress for Patients Funds), PI: Nicole Urban; **Role on project: Project Leader, wrote proposal and directed trial**, 2004-2007, \$496,238.
- ALPHA Trial: Alberta Physical Activity and Breast Cancer Prevention Trial. Canadian Breast Cancer Research Initiative, PIs: Christine Friedenreich and Kerry Courneya; **Role on project: Co-Investigator**, 2002-2007, \$1,104,147.
- Mammographic Density and Invasive Breast Cancer, PI: Etta Pisano, **PI of FHCRC Subcontract: Anne McTiernan**, R01 CA105007-01, 2004-2007, \$50,524 (direct).
- Cognitive Effects of Aerobic Exercise for Adults with Impaired Glucose Tolerance: A Controlled Trial (American Diabetes Association), PI: Laura Baker; **Role on project: Co-Investigator**, 2004-2007.
- Cognitive Effects of Aerobic Exercise for Adults with Mild Cognitive Impairment: A Controlled Trial (Alzheimer's Association), PI: Laura Baker; **Role on project: Co-Investigator**, 2004-2007.
- Social and Physical Activity of Childhood Cancer Survivors, PI: Debra Friedman; **Role on project: Co-Investigator**, NIH/NCI CA 104123-01A2, 2005-2007, \$107,500.
- UW Multidisciplinary Research Training Grant, PI: R Deyo; **Role on project: Co-Investigator, Mentor**, 1 K12 HD 49100-01, 2004-2009, \$1,172,239.
- Epidemiology of Gallbladder Sludge and Stones in Pregnancy, PI: Sum Lee; **Role on project: Co-Investigator**, RO1 DK46890, 2003-2008, \$372,840.
- Breast Cancer Prognostic Factors/Pathobiology by Age, PI: Kathi Malone; **Role on project: Co-Investigator**, NCI-1 R01 CA098858-01A2, 2004-2009.
- Seattle TREC Center, **PI: Anne McTiernan**, NIH/NCI U54 CA116847, 09/23/2005 – 08/31/2011, \$12,612,045.
- Exercise, Diet, and Postmenopausal Sex Hormones, **PI: Anne McTiernan**, NIH/NCI R01 CA105204, 09/01/2004 – 06/30/2011, \$3,348,605.
- Reducing Obesity at the Workplace: A Randomized Trial, PI: Shirley Beresford; **Role on project: Co-Investigator**, NIH/NHLBI R01 HL079491, 7/1/2004-6/30/2011.
- Effect of Exercise and Weight Loss on Adipose Tissue Biology, **PI: Anne McTiernan**, NIH/NCI R21 CA131676, 05/01/2008 – 04/30/2011, \$435,600.
- Effect of Dietary Intervention on Insulin and IGF-1 Receptors in Prostate Cancer (Pacific NW Prostate SPORE pilot project), **PI: Anne McTiernan**, NIH/NCI P50 CA97186, 09/01/2009 – 08/31/2011, \$48,836.
- Alberta Physical Activity (ALPHA) and Breast Cancer Prevention Trial: an ancillary study examining androgens, biomarkers of obesity, and inflammation. Alberta Breast Cancer Research Initiative, PI: CM Friedenreich; **Role on project: Co-Investigator**, \$170,000.
- Bid & Proposal Funds to Assess Baseline Body Composition, by Dual X-ray Absorptiometry (DXA), in Participants of an Ongoing Clinical Trial (Vitamin D, Diet & Activity Study, ViDA) **PI: Anne McTiernan**, 12/1/2010 – 06/30/2011, \$16,000 (direct).
- A Phase III Randomized Controlled Study of Exemestane Versus Placebo in Postmenopausal Women at Increased

Risk of Developing Breast Cancer. **PI of FHCRC Clinic: Anne McTiernan**, National Cancer Institute of Canada, 10/2004 – 11/2012, \$1,631,150.

- Komen Scientific Advisory Council Award “Vitamin D, Weight Loss, and Breast Cancer Biomarker,” **PI: Anne McTiernan**, SAC110024, 07/01/2010 – 06/30/2012, \$500,000.
- Weight Loss & Exercise Effects on Telomere Length in Postmenopausal Women, **PI: Anne McTiernan**, NIH/NCI R21 CA155823, 12/14/10 – 11/30/12, \$428,705.
- Oxidative Stress in Chronic Kidney Disease, University of UW PI: Jonathan Himmelfarb; **Role on project: PI of FHCRC subcontract**, NIH/NHLBI R01 HL070938, 01/01/2011 – 12/31/2012, \$197,630 (FHCRC only).
- Komen Scientific Advisory Council Award “Vitamin D, Weight Loss, and Breast Cancer Biomarker,” **PI: Anne McTiernan**, SAC110024, 07/01/2012 – 06/30/2013, \$225,000.
- NCI: Exercise Effects on Serum Biomarkers of Angiogenesis, PI: Catherine Duggan, PhD; **Role on Project: Co-Investigator & Mentor**, NIH/NCI R03 CA152847, 04/01/2011 – 03/31/2013, \$176,000.
- HEAL Follow-up, NIH/NCI Contract. Manuscript Development for the HEAL Study of Breast Cancer Prognosis, **PI: Anne McTiernan**, NCI contract, 10/2012-9/2013
- Vitamin D Effect on Body Composition During Behavioral Weight Loss in Women, **PI: Anne McTiernan**, NIH 1R03CA162482, 04/01/12 – 03/31/14, \$175,000
- Effect of Vitamin D and Weight Loss on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/13-9/30/14, \$230,378.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/14-9/30/15, \$250,000.
- Weight Loss & Cancer Biomarkers in Women: Oxidative Stress & Inflammation, **PI: Anne McTiernan**, NIH/NCI, 1R01CA161131, 04/15/2012 – 9/30/2015, \$863,179.
- Safeway Foundation Assessing Vitamin D, Weight Loss and Breast Cancer Risk Factors, Safeway Foundation, PI: Catherine Duggan, PhD; **Role on Project: Co-Investigator & Mentor**, 7/1/2013 – 6/30/2014, \$36,000 (in NCE).
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/15-9/30/16, \$250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/16-9/30/17, \$250,000.
- Methods for Measurement Error in Physical Activity & Diet, PI: CY Wang; **Role on Project: Co-Investigator**, NIH/NHLBI R21HL121347, 12/1/13-12/31/16, \$494,493.

Active

- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/17-9/30/18, \$250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/18-9/30/19, \$250,000.
- INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A Multicenter, Randomized, Controlled, Phase III Study, PI: Jonathan Wright; **Role on Project: Co-Investigator**, November, 2016 - .
- Exercise Effects in Men & Women on Colon DNA Methylation, **PI: Anne McTiernan**, NIH/NCI 1R21CA209203-01A1, 3/15/17 – 2/28/19, \$421,080.
- Exercise Effects in Men & Women on Colon DNA Methylation, **PI: Anne McTiernan**, NIH/NCI 1R21CA209203-01A1, 3/15/17 – 2/28/19, Administrative supplement, \$176,000.
- Impact of an exercise program in cancer patients on chemotherapy treatment, **PI's: Anne McTiernan & Blair Irwin**, Ben Greer SCCA Pilot Study Funds, 9/17-8/18, \$50,000 (no cost extension).
- Longitudinal Weight Data from Two Behavioral Weight Loss Randomized Controlled Trial, **PI: Anne McTiernan**, FHCRC Bid & Proposal Funds, 10/17-9/18, \$15,000.
- The effects of moderate exercise on distress, quality of life, and biomarkers of angiogenesis and chronic stress in ovarian cancer survivors, NCI R21CA215662-01A1, PI: Kathryn Pennington; **Role on Project: Co-Investigator**

TEACHING/MENTORING

Junior Faculty

Katy Pennington, MD (School of Medicine, OB/GYN, University of Washington)
Holly Harris, PhD (Epidemiology Program, PHS, FHCRC)
Catherine Duggan, PhD (Epidemiology Program, PHS, FHCRC)
Blair Irwin, MD (Multi-Care, Tacoma, SCCA affiliate)
Jonathan Wright, MD, MPH (School of Medicine, Urology, University of Washington & Epidemiology Program, PHS, FHCRC)

Postdoctoral Fellows

1. Melinda Irwin, PhD (current Full Professor, Yale University)
2. Melanie Palomares, MD, MPH (current faculty City of Hope, Los Angeles)
3. Laura Frank, PhD
4. Page Abramson, PhD
5. Karen Foster-Schubert, MD (current Assistant Professor, U. of Washington)
6. Kristin Campbell, PhD (current Assistant Professor, U. British Columbia)
7. Lisa Cadmus, PhD (current staff scientist U. C. San Diego)
8. Ikuyo Imayama, MD (current medical resident, Seton Hall University, St. Francis Medical Center, Trenton, NJ)
9. Caitlin Mason, PhD (current postdoctoral fellow, FHCRC)

Additional Postdoctoral Fellows Working with My Studies' Data

10. Jean De Dieu Tapsoba, PhD (current postdoctoral fellow, FHCRC; primary mentor is CY Wang, PhD)
11. Aaron Thrift, PhD (current postdoctoral fellow, FHCRC; primary mentor is T. Vaughan, MD)

PhD Committees and Predoctoral Trainee Mentoring

1. Lisa Godefroy Johnson (member of PhD committee)
2. Shelley Slate Tworoger (member of PhD committee)
3. Cara Frankenfeld (member of PhD committee)
4. Victoria M. Chia (member of PhD committee)
5. Lori Williams (member of PhD committee)
6. Angela Kong (co-chair of PhD committee)
7. Babbette Saltzman (member of PhD committee)
8. Anita Iverson (visiting Norwegian predoctoral student 2009-10, advising)
9. Adriana Villasenor (member of PhD committee)
10. Sissi Espetvedt Finstad, MD (Norwegian PhD student, advising)

MS and MPH Committees

1. Margaret Krieg, MD (member of MPH committee)
2. Sylvia Young, MD (chair of MPH committee)
3. Jana Pruski (chair of MPH committee)
4. Melanie Palomares (chair of MPH committee)
5. Susan Stanford (member of MPH committee)
6. Melinda Irwin, PhD (chair of MPH committee)
7. Andrew Shors, MD (member of MPH committee)
8. Libbby Morimoto (member of M.S. committee)
9. Breanna Mitchell (member of M.S. committee)
10. Erin Aiello (chair of MPH committee)
11. Erin Shade (member of M.S. committee)
12. Julie Meyers (member of M.S. committee)
13. Manish Mohanka (chair of MPH committee)
14. Vivian Hawkins (chair of MPH committee)
15. Isaac Rhew (member of MPH committee)
16. Ann Ready (member of MPH committee)

17. Alanna Boynton (member of MS committee)
18. Heather Hildebrandt (member of MPH committee)
19. Jo Henderson (chair of MPH committee)
20. Laura Hooper (member of MPH committee)
21. Kristen Sipsma (member of MPH committee)
22. Karen Foster-Schubert (chair of MS committee)

Advising: Medical Students Research (University of Washington ISMS): Jennifer Rupert, Erin Griffith, Kelley D. Pratt, Maegan Ashworth

Post-Graduate Physician Training in Cancer Prevention & Control (FHCRC): Elliott Rosenberg, MD, MPH, Mary Ann Gilligan, MD, MPH, Maureen Brown, MD

Formal Career Development Mentoring: Karen Foster-Schubert, MD, University of Washington NIH K-12 Fellow 2005-2010; Karen Mustian, PhD University of Rochester NCI Cancer Control Clinical Research Training Program 2004-

FHCRC scientists mentoring: Neli Ulrich, PhD, Rebecca Rudolph, MD, MPH, AnneClaire DeRoos, PhD, Alyson Littman, PhD, Jonathan Wright, MD, MPH, Catherine Duggan, PhD, Larissa Korde, MD

Individual Study Credits

<u>Course</u>	<u>Title</u>	<u>Credits</u>	<u>Years</u>
Epi 499	Undergraduate Research	Var	1997-2005
Epi 600	Graduate Study/Research	Var	1997-2005
Epi 700	Masters Research	Var	1998-2005
Cancer Epi	guest lecture	1999, 2002-2005	

Continuing Medical Education Teaching

- Breast Cancer in Young Women, University of Washington Continuing Education Conference, August 6, 1994, Depts. of Surgery and Medicine.
- Current Concepts in the Early Detection of Breast Cancer, Multicare, Madigan Army Medical Center, and American Cancer Society 3rd Annual Oncology Conference, April 11, 1995.
- Current Concepts in Breast Cancer – 1997, University of Washington Continuing Medical Education, October, 1997, 1999, 2000 (session moderator), 2001, 2003, 2009, 2010
- “Update to the Women’s Health Initiative” March 18, 2001, University of Washington talk to IM, GYN, FM residents.

Clinical Teaching (U. of Washington School of Medicine)

- Attending Physician, Adult Medical Center, Harborview Medical Center, 1992-95 – supervised internal medicine residents in primary care setting.
- Mentoring and training geriatric fellow, Dr. Michi Yukawa, in exercise tolerance testing and testing VO2 max (1999)

Other Academic

Primary Opponent, PhD Thesis Defense, Aina Emaus, University of Oslo, Norway (thesis chair, Inger Thune) 2009

FHCRC SERVICE

- Director, Prevention Center Shared Resource, 2001-2012
- Chair or Member of several faculty promotion committees and 5-year review committees
- Reviewer for CCSG renewal: 2013, 2018
- Member, Scientific Advisory Committee for the Seattle Cancer Care Alliance Prevention Clinic
- Member, Research Trials Office Oversight Committee, 2003 – 2005
- Member, Fred Hutchinson Cancer Research Center Institutional Review Board, 1984-5; 2002 - 2003
- Member, FHCRC Health Care Task Force, 1996
- Member, Clinical Protocol Scientific Review and Monitoring Committee, 1996- 1997
- Organizer, FHCRC Public Health Sciences Hormone Special Interest Group 1995-96
- Member, Seattle Breast Cancer Program Executive Committee, 1998 - 2000
- Member, Ad-Hoc Committee on Improvements in Public Health Sciences Procedures, 1998
- Member, CSS Advisory Committee, 1999 – 2000

- Nutritional/Hormonal Biomarkers group, 2001 – 2002
- Member, CDS Users Group, 2001 – 2002

UNIVERSITY OF WASHINGTON SERVICE

- Reviewer, Royalty Research Fund, Spring, 1997
- U. Washington Breast Cancer Update 2000 Continuing Medical Education – session moderator

PROFESSIONALLY-RELATED COMMUNITY SERVICE

- Medical Advisory Board, Team Survivor Northwest 1997-
- Professional Advisory Committee, Breastcancer.org, 2003-

LAY AUDIENCE PRESENTATIONS

- National Council of Jewish Women, Seattle Section, “Women’s Health Initiative”, Nov 1992
- Nordstrom’s “Face of Breast Cancer” breast cancer awareness seminar, October 1997
- Danskin Women’s Triathlon, 8/15/98
- Afternoon of Hope, Horizon of Hope National Charity Campaign, Longaberger Co., FHCRC, 8/29/98
- Media roundtable, Women’s Health Initiative, December, 1995
- Breast Cancer Forum: Clinical Implications of Current Research, FHCRC, 10/8/98
- Women’s Health Issues Panel, The Healthy Living Expo, Seattle, WA, 2/7/99
- Virginia Mason Hospital Breast Cancer Support Group “Weight Control and Cancer Survival” September 1999.
- FHCRC Volunteer Conference “Breast Cancer Risk Factors” May 2000.
- FHCRC Women’s Health Series “Exercise and Breast Cancer” April 2000.
- Bellevue Rotary Club, “Exercise and Breast Cancer” October 2000.
- Cardio Pulmonary Rehabilitation Institute Oncology Rehabilitation, Lubbock Texas, “Exercise for Breast Cancer Prevention and Rehabilitation”, March 2001
- Greater Cincinnati Breast Cancer Association, October 2001.
- FHCRC Community Lecture "Exercise for Breast and Colon Cancer Prevention" November 2001
- Providence/St. Vincent Medical Center, Portland, OR October 2003
- Women’s Health Day, Anchorage, Alaska 2005
- Cancer Wellness Center, Northbrook, IL 2005

MEDIA

- Media (TV) interviews on physical activity, obesity, vitamin D, sleep, cancer: Today Show (NBC); MSNBC News Show; ABC News w/Peter Jennings; ABC World News Tonight; CBS Evening News; CBS News; Seattle KOMO, KIRO, KING, FOX13; WZTV-FOX, KOCO-ABC, WFLA-NBC, WBTB-CBS, WLUC-FOX
- Media (radio): KJZZ, Canadian health radio talk show; numerous Seattle-area radio interviews
- Media (print) –Prevention Magazine, American Health Magazine, Time Magazine, Parents’ Magazine, Family Circle, Associated Press, Time, Women’s World, Cosmopolitan, Glamour, Self, Reader’s Digest, New York Times, Wall Street Journal, LA Times, Parade Magazine, Seattle Times Pacific Magazine, USA Today, U.S. News and World Report, Health Magazine, Seattle Magazine, Self, More and others
- Several on-line news media each year
- “Preventing Breast Cancer” written commentary for ABC.com, April 2002.
- Ivanhoe National TV Productions specials on Breastfeeding, Breast Cancer, and Breast Gel Study September 2002

Exhibit 3

Statement of Dr. Anne Mc Tiernan prepared for the Subcommittee on Economic and Consumer Policy Hearing on Examining the Public Health Risk on Carcinogens and Consumer Products, March 12, 2019

Chairman Krishnamoorthi, Ranking Member Cloud, and members of the subcommittee, good morning and thank you for inviting me. My name is Dr. Anne McTiernan. I am a cancer prevention researcher in the Epidemiology Program, Division of Public Health Sciences, at the Fred Hutchinson Cancer Research Center in Seattle, Washington. I am also a Research Professor in the University of Washington Schools of Public Health and Medicine. I am not representing the Fred Hutchinson Cancer Research Center or the University of Washington in the presentation of my testimony to the Subcommittee. I am an internal medicine physician and epidemiologist. My research focuses on cancer epidemiology and prevention, particularly cancers in women. I was asked to give testimony today because I have conducted a thorough and systematic review of the science linking use of talcum powder products and risk for ovarian cancer. As part of this review, I prepared an expert report on behalf of consumers for an ongoing multi-district litigation on talcum powder products as causes of ovarian cancer.

My scientific review focused primarily on the epidemiologic research. Epidemiologists look at large groups of people with a disease, and compare them to people without that disease, to find what might be causing the disease.

The American Cancer Society and the U.S. National Cancer Institute estimate that in 2019, 22,530 women will receive a new diagnosis of ovarian cancer and 13,980 women will die from ovarian cancer.(1, 2) There is no established method to screen for early ovarian cancer. As a result, most women are diagnosed at an advanced, less treatable stage. There is also no

established method to prevent ovarian cancer other than surgical removal of ovaries. Therefore, it is critical to identify causes of ovarian cancer in order to prevent this serious disease.

My review identified 38 high-quality epidemiologic studies conducted over the past 40 years.

These studies asked women about their use of talcum powder products in the genital area, and tested associations with risk of ovarian cancer. Together, these studies included over 14,000 women with epithelial ovarian cancer (the most common type) and an even greater number of women without ovarian cancer. Most of these studies were conducted in the United States.

Ovarian cancer is thought to develop over years. Therefore, a woman's exposures in her young and middle years can affect her risk of ovarian cancer decades later. Women have reported use of talcum powder products on sanitary napkins, underwear, and directly to the genital area. In some studies, over 4 in 10 women report ever regularly using these products in the genital area.(3)

Summarizing data from all of the published studies consistently shows that women who had ever used talcum powder products in the genital area had a statistically significant 22 - 31% increased risk of developing epithelial ovarian cancer compared with women who had never used them.(4-6) Evidence suggests that these associations hold across diverse race and ethnic groups.

These combined analyses showed that increasing amount of exposure to talcum powder products in the genital area resulted in increasing risk of developing epithelial ovarian cancer.

Published laboratory and clinical studies provide evidence that in humans, talc can migrate from the genital area to the ovaries and fallopian tubes. Talc has been shown to cause an

inflammatory response in the human body. Elevated levels of inflammation in women are associated with increased risk of ovarian cancer. All of this provides a biologically plausible pathway by which talcum powder product exposure can cause ovarian cancer.

Given the frequency with which asbestos has been found in cosmetic and personal use talc products, I reviewed the literature on the epidemiology of asbestos and risk of ovarian cancer. In 2012, the International Agency for Research on Cancer stated that a causal association between exposure to asbestos and cancer of the ovary was clearly established.⁽⁷⁾ That agency has also classified fibrous talc as a Class 1 carcinogen – the most dangerous level of carcinogen.

Given the high prevalence of use of talcum powder products, a 22 - 31% increase in risk can have profound effects on clinical events and public health. Women need to know about the risks of using talcum powder products in their genital areas. All consumers need to be warned about the contents of these products, including asbestos and fibrous talc, so that they can make informed decisions about use.

Thank you for the opportunity to provide this testimony. I would be happy to answer any questions you may have.

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Exhibit 4

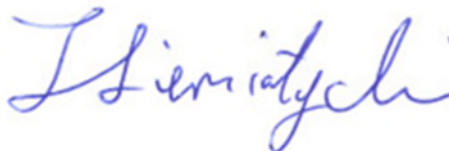
**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
JACK SIEMIATYCKI MSc, PhD**



Date: November 16, 2018

Jack Siemiatycki MSc, PhD

EXPERT REPORT OF JACK SIEMIATYCKI MSc, PhD
On
TALCUM POWDER USE AND OVARIAN CANCER

Jack Siemiatycki, MSc, PhD, FCAHS

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November 16, 2018

TABLE OF CONTENTS

1. My mandate.....	1
2. My credentials, expertise and experience	1
3. Overview of my methodology.....	4
4. The science of epidemiology.....	5
4.1 Some basic measures and notions used in epidemiology	6
4.2 Bradford Hill “guidelines”	18
5. Epidemiologic evidence regarding talc and ovarian cancer	23
5.1 IARC review and evaluation of talcum powder products.....	23
5.2 Information consulted for the present review.....	25
5.3 My methodology for this review.....	26
5.3.1 Selecting studies for review	26
5.3.2 What were women exposed to in body powders?	29
5.3.3 Routes of exposure	31
5.3.4 Questionnaire items on use of talc powders	32
5.3.5 Metrics of exposure	33
6. My meta-analyses regarding talcum powder products and ovarian cancer: data included and results	33
6.1 Features of the studies.....	33
6.2 Association between binary variable talc powdering and all types of ovarian cancer combined – data and results	34
6.2.1 Individual studies and results on binary exposure variable	34
6.2.2 Strategy for Main analysis and sensitivity analyses.....	35
6.2.3 Results of meta-analyses on binary exposure variable for all ovarian cancers.....	38
6.2.4 Other contemporaneous meta-analyses on binary exposure variable for all ovarian cancers.....	39
6.3 Dose-response – cumulative exposure, duration and frequency.....	42
6.4 Subtypes of ovarian cancer - in particular, serous invasive tumors	45
6.5 Conclusion from meta-analyses and dose-response considerations	47
7. Misconceptions and possible biases	47
7.1 Some prominent misconceptions in reviewing the evidence	48
7.2 Alternative explanations - Biases and errors.....	53
7.2.1 Bias due to non-response or non-participation.....	53
7.2.2 Recall or reporting bias.....	54
7.2.3 Non-differential (or random) error in recall or reporting of exposure to powders.....	55
7.2.4 Short follow-up periods for disease ascertainment.....	57

7.2.5	Diagnostic error	57
7.2.6	Initiation of powdering as a result of ovarian cancer.....	58
7.2.7	Confounding	59
7.2.8	Publication bias	60
7.2.9	Summary comments regarding biases and errors	61
8.	Bradford Hill guidelines applied to talc and ovarian cancer	61
9.	Contrast with IARC Monograph and other reviews	67
10.	Conclusion.....	69
11.	Tables	70
12.	Figures.....	90
13.	Appendix A.....	94
14.	Appendix B.....	103
15.	Appendix C.....	107
16.	References	109
	Bibliography Part A: Documents available in the Public Domain	110
	Bibliography – Part B: Documents not available in the Public Domain.....	127
17.	Curriculum Vitae – Jack Siemiatycki	141

1. My mandate

I have been retained to assess the epidemiologic evidence regarding the **general causation** between perineal (or genital) use of talcum powder products and risk of ovarian cancer. The question is: "Can application of talcum powder products in the perineal region cause ovarian cancer?"

All of my opinions in this report are stated to a reasonable degree of scientific certainty.

2. My credentials, expertise and experience

I am a tenured Professor of epidemiology at the University of Montreal and an Adjunct Professor of epidemiology at McGill University in Montreal. I have received prestigious national research awards in Canada, such as National Health Scientist Salary Award, Medical Research Council Distinguished Scientist Award, Canada Research Chair in Environment and Cancer and, currently, I hold the Guzzo-Cancer Research Society Chair in Environment and Cancer. I am an elected fellow of the Canadian Academy of Health Sciences. I was awarded a lifetime achievement award by the Canadian Society for Epidemiology and Biostatistics, the premier professional organisation in our discipline.

Trained in statistics and in epidemiology, I have devoted most of my research career to investigating links between environmental, occupational and lifestyle factors and various types of cancer. My research has been both substantive – namely, looking at particular factors and their possible relationship to particular cancers - and methodological – namely, exploring how to evaluate and enhance the validity of epidemiologic research through various prisms: study design, data collection methods and statistical analysis. Of my approximately 250 research publications, about one quarter would be considered to have methodological focus.

I have held various leadership positions, including the elected presidency of the Canadian Society for Epidemiology and Biostatistics, and elected membership on the Board of the American College of Epidemiology. I have been invited to serve on over 160 Boards, Scientific Councils and Expert Panels for a host of governments, universities or research agencies. Examples include: Board of Directors of the Canadian National Cancer Institute, member of expert panel tasked with recommending priorities for action under the

Canadian Environmental Protection Act, member of external peer review panel of the Epidemiology branch of the US National Cancer Institute (NCI), member of two different expert advisory bodies to research projects at the NCI, consulted by President Clinton's Cancer panel, member of external peer review panel for the Helmholtz German national medical research agency, Chair of the Scientific Council of the largest prospective study of causes of cancer being conducted in France, and others of that nature.

I have been associate editor of the American Journal of Epidemiology and the International Journal of Environmental Health. In addition, I have served as reviewer for about 20 journals. I have served as a chair and as a member of grant review panels for major Canadian scientific funding agencies.

My research programme has been well funded by Canadian funding agencies for over 35 years. I have conducted research and published on the carcinogenicity of a large number of agents in the occupational environment (e.g. asbestos, silica, welding fumes) and in the general environment (e.g. smoke from wood stoves, urban air pollution) and lifestyle factors (e.g. smoking, alcohol, use of cell phones).

I have taught and supervised epidemiology students and many of my former trainees are now faculty members in universities around the world.

I have had a long association with the International Agency for Research on Cancer (IARC). IARC is the premier institution in the world for cancer epidemiology and for environment and cancer research. It has several mandates, including the organisation and compilation of standardised high quality data on cancer incidence around the world, the conduct of original research, and the evaluation of the carcinogenicity of different agents with which humans come into contact. The latter is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens. Since the inception of this program in 1971, there have been about 120 meetings held and approximately 1100 agents have been evaluated.

A particular point of pride for me is that over the years, research results from my team have been cited as part of the information base on 69 of the 1100 agents that have been evaluated, probably making my team the most cited epidemiology team in the history of the IARC Monograph program.

My association with IARC began when I did a post-doctoral fellowship there in 1977-79. Over the intervening years I have collaborated with scientists at IARC on various research projects. I was a member of the 18-member Scientific Council of IARC from 2006 to 2010 including two years as elected Chairman of the Council. The Scientific Council oversees all of the scientific activities at IARC; its members are named by the member states of IARC. I have been invited to sit on IARC Monograph international expert panels for 5 of the 60 panels convened in the past 25 years. One of the IARC Monograph panels of which I was a member was tasked with evaluating: "Carbon black, titanium dioxide and non-asbestiform talc." Out of the 16 invited experts who participated in the meeting as members of the Working Group, I was selected to chair the meeting.

Subsequent to the IARC meeting and the report of the meeting, a small subgroup of members of the IARC Working Group, of which I was a member, conducted and published a meta-analysis of the results of the studies that had been available to the IARC Working Group (Langseth, 2008)

Although I have not personally produced original data collection studies on the topic, I am well qualified to review the epidemiologic evidence. I have participated in two published reviews of the issue. The methodologic expertise and analytical skills required to critically review and evaluate such evidence is generic to the vast area of environmental epidemiology of cancer. I am routinely asked by journals and grant agencies to provide expert opinions on topics for which I have not produced original data collection studies, but that are within the purview of my expertise. The invitation by IARC to chair the meeting at which talc was evaluated is testimony to the fact that my competence and expertise in this matter are internationally recognized by peers. I do not claim expertise in various adjoining domains that inform this issue, including physiology, pathology, clinical oncology, experimental toxicology, geology and mineral chemistry. However, I do have the

expertise and skill to assimilate information that is provided by experts in these areas. I have previously submitted a report on my review of the evidence regarding talcum powder products and ovarian cancer in October 2016.

I have previously served as an expert witness for plaintiffs in one U.S. court case, and that was a talc litigation in Los Angeles in 2017. (Eva Echeverria, BC628228, Johnson and Johnson Talcum Powder Cases, CA JCCP No. 4872), and I testified that the genital use of talcum powder products can cause ovarian cancer.

I have served as an expert witness in two Canadian court cases, neither having to do with talc or hygiene powders or ovarian cancer. One case dealt with a class action lawsuit on behalf of a town in Canada adjoining a Canadian military base where there had allegedly been a spill of trichloroethylene that seeped into the water table of the town. The residents claimed that the contamination had caused cases of cancer. I was an expert for the defence, the Canadian government, and I testified in 2012. (Province of Quebec Superior Court file 200-06-000038-037).

The other case was a class action on behalf of Quebec residents who contracted cancer and had been smokers, claiming that the tobacco companies were responsible for their diseases. I was an expert for the plaintiffs and I testified in 2014. (Province of Quebec Superior Court file 500-06-000076-980).

In my work as an expert for legal cases, my time is billed at the rate of \$450 per hour for research, report preparation, communications with counsel, participation in depositions, and testimony in court.

3. Overview of my methodology

The basis of my opinions derive from my education, training, experience, research and what is accepted within the community of leading scientists practicing in the field of epidemiology. My opinions are based on my review of the relevant materials, published in the scientific literature and/or produced in this case; including internal company documents, as well as relevant depositions, reports and testimony in the talcum powder product litigation. To reach my conclusions, I have employed the same scientific

methodology and rigor that I use in my research, in my publications and in the consulting and advising that I carry out on behalf of governments, public health agencies and research institutes. This includes a review of the relevant published literature, expert judgment to assess the quality and meaning of the various studies that were reviewed, and syntheses of the available evidence and any other pertinent medical and scientific evidence of which I am aware. The methods I used to derive and present my opinions are those used in general in the assessment of causal relations in medicine and public health, and more specifically in epidemiology. The methods are based on the experience and insight I have accumulated over 40 years of research, consulting, reviewing and student supervision, from discussions and interactions with leading epidemiologists, service on multiple IARC panels, and from reading evolving ideas in the scientific literature, including such seminal works as Bradford Hill's (Hill 1965) writings on assessing causality.

My opinions may be further supplemented and refined, subject to results that may come from further medical and scientific study and research and the continued review of additional information and discovery materials produced in this litigation.

4. The science of epidemiology

This section is designed to provide a non-specialist reader with information and definitions about epidemiology and biostatistics that are needed to understand the basis of my evaluation on talcum powder products and ovarian cancer. I do not present in this section the actual data and evidence regarding talcum powder products and ovarian cancer.

Epidemiology is the science of occurrence of diseases in human populations. It is concerned with the patterns of disease occurrence and also with identifying the factors that influence disease occurrence. These two sets of concerns are sometimes referred to respectively as descriptive epidemiology and analytic epidemiology. The first addresses such issues as the incidence of the disease in different geographic areas, in different time periods, or at different ages and sexes. The second addresses more focused questions on the specific environmental and/or lifestyle and/or genetic factors that might influence the incidence of disease.

The word “epidemiology” has the same etymologic roots as the word “epidemic”, which signifies that, initially, epidemiology grew out of the study of epidemics. Such epidemics were often of a microbial origin (e.g. viruses, bacteria, parasites). But increasingly in the 19th and especially in the 20th century, it became clear that the etiology (i.e. causation) of chronic diseases such as cancer could also be elucidated by studying their patterns of occurrence.

While there were many studies carried out in the early to mid-20th century that we would now qualify as epidemiological in nature, the discipline of epidemiology and its methods started to become formalized in the 1950’s and 1960’s. There are now departments of epidemiology in most large universities that have health science research and teaching activities and there are many national and international societies of epidemiology.

Epidemiology is characterized by its mainly observational and non-experimental approaches. It is a discipline that is not primarily based in the laboratory; rather it is based in society. That is the source of its strength, and its weakness. Because it deals with people in the reality of their lives, it is the most pertinent approach to understanding the links between people’s lifestyles and environments and their health and disease. However, because it is based in society, it by necessity confronts the extreme complexity of human lifestyles, environments and diseases. And because we cannot experiment with people’s lives, we cannot control the conditions in which people are exposed. The methods of epidemiologic research are complex and differ from study to study. Statistical methods play an important role in trying to tease out the role of different variables and in determining whether the observed results may be attributable to chance, to bias or to real effects of putative risk factors. It is usually necessary to assemble evidence from several data-collection studies on a given topic before being able to draw inferences about causality.

4.1 Some basic measures and notions used in epidemiology

In this section I will review a number of concepts that need to be understood in order to properly understand my review of the evidence regarding talc powder and ovarian cancer. It is intended for readers who may not be expert in epidemiology. In this section I will not necessarily tie the concepts and definitions to the talc-ovarian cancer issue; that part will

be left for later. For now, I am simply introducing the non-epidemiologist reader to terminology and concepts with which she/he may not be very familiar.

Prevalence of disease. The prevalence of a disease refers to the proportion of a population who are living with the disease at any given point in time.

Incidence of disease. The incidence of a disease refers to the proportion of a population who are newly diagnosed with the disease during a certain period of time. The bridge between incidence rate and prevalence rate is the average duration of the disease, or how long people live with it before they are cured or pass away. In fact, while incidence and prevalence are foundational concepts in epidemiology, it is only incidence that figures prominently in the evaluation of carcinogenicity of talc.

Risk of disease. The risk of disease is a term that can refer to incidence or prevalence. The meaning should be clear from the context in which it is used. For studies of cancer, it almost always refers to incidence of disease. This is the way I will use the term in this report.

“Cause” of disease. A cause of a disease is any agent or characteristic (environmental, lifestyle or genetic) that increases the probability of getting the disease or it may simply advance or hasten the onset of the disease. It may act alone or it may act in concert with other factors over a lifetime to cause the disease. It may act immediately (e.g., cyanide as a cause of poisoning; lack of seat belt use as a cause of car accident mortality) or it may take many years for the effect to become manifest (e.g., lack of physical activity as a cause of obesity). There may be many different causes for the same disease. (See explanation of Multifactorial Etiology below.)

Risk factor. As defined in the Dictionary of Epidemiology (Last 2001), a risk factor is an aspect of personal behavior or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with a health-related condition. The term *risk factor* is used rather loosely and depending on the context it can refer to a factor that directly causes a disease or a factor that is a strong marker for the proximal cause of the disease. As it is often used, I will

mainly use the term “risk factor” as a synonym for the noun “cause” of the disease. (eg. “Smoking is a risk factor for lung cancer.”)

Association. As defined in the Dictionary of Epidemiology (Last 2001), association refers to the degree of statistical dependence between two or more events or variables. Events are said to be associated when they occur more frequently together than one would expect by chance. Association does not necessarily imply a causal relationship.

Risk among unexposed (R_u) refers to the risk of disease among persons who are not (or were not) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have never* used talc in the perineal region.

Risk among exposed (R_e) refers to the risk of disease among persons who are (or were) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have* used talc in the perineal region.

Relative Risk: $RR = R_e/R_u$ = Risk among exposed/Risk among unexposed

When $RR > 1.0$, it indicates that exposure to the agent increases the risk of developing the disease. When $RR < 1.0$, it indicates that exposure to the agent prevents the disease.

When $RR = 1.0$, it indicates that the exposure to the agent has no bearing on the risk of getting the disease.

95% Confidence interval (95% CI). This refers to the precision of an estimate of a parameter. When we estimate the 95% CI for the RR, we are approximately saying that we are 95% certain that the true parameter underlying the study is within these limits. (The true interpretation is more subtle.)

Statistical significance of an association: Statistical significance is a measure of the departure of a set of data from some null hypothesis. Most commonly in epidemiology, the null hypothesis would state that there is no association between a factor and a disease. The null hypothesis can be operationalized in different ways, such as that the $RR = 1.0$, or that there is no trend between the degree of exposure and the RR. Once a study is conducted, the results can be compared with the expected results based on the null hypothesis, and the discrepancy from the null hypothesis is measurable with probabilities. This is done

either by computing a p-value or a confidence interval. If the p-value is very small or the confidence interval does not include the null value, then we say that an observed association between the putative risk factor and the disease is unlikely to be due to chance alone.

It is important to note that while statistical significance is a tool for assessing whether an observed association is attributable to chance alone, it is not a very effective tool for establishing the absence of an association. That is, the absence of statistical significance is not tantamount to proof of the absence of an association. The absence of statistical significance can be due to the true absence of an association, but it can also be due to the study not having sufficient statistical power or to bias or confounding in the research methods. Furthermore, it should be noted that the conventional dichotomization of results as “statistically significant” or not, based on a particular cutpoint on the p-value scale (eg. $p = 0.05$), is a gross simplification. The compatibility of the data with the null hypothesis of no association is in truth on a continuous scale and the dichotomization is arbitrary and potentially misleading, especially when the observed p-value is close to the arbitrary cutpoint.

In practice, epidemiologists have been moving away from using and reporting p-values and statistical significance, as it has become clear that the main contribution of an individual study is to provide an estimate of the relative risk and its range of plausible values, embodied in a confidence interval.

Cohort studies and case-control studies: Epidemiologic research projects can take many different forms. The two most common types of analytic epidemiologic studies are cohort studies and case-control studies. (Rothman, Greenland, & Lash 2008)

In a cohort study, it is typical to enrol a large number of subjects, determine which ones are or have been exposed to the factor of interest (e.g., talc) and follow them for some period of time to evaluate whether those who were exposed subsequently experienced different disease rates from those who were not exposed.

In a case-control study, by contrast, we start with people who have the disease under study (e.g. ovarian cancer) and a set of controls who do not have the disease, and we collect data

to determine whether the cases and the controls had different histories of exposure to the factor under study (e.g. talc).

It may be said that a cohort study proceeds from the cause to the effect, whereas a case-control study starts from the effect and backtracks to the cause. There are many variants on these basic designs. These descriptions of these types of study are somewhat simplified.

It is sometimes claimed that a prospective cohort design produces more valid and reliable RR estimates than a case-control study. But this is incorrect as a generalization. The validity and reliability are not determined by the overall architecture of the study, but rather by the specifics of the study, including how the study subjects were assembled, the nature of the variables under study (exposure, disease, confounders), exactly how the information was collected, the statistical power, and so on. There may be many reasons why a particular case-control study is more valid than a particular cohort study.

Relative Risk (RR) and Odds Ratio (OR). The cohort study design leads naturally to the estimation of risk of disease among exposed, and risk of disease among unexposed, and then to the ratio of those two, which is the RR. In case-control studies, because of the way the study samples are selected, it is impossible to estimate the risk of disease or the ratio of the two risks, R_e/R_u . However, under certain conditions which are well met in studies of cancer, it is possible to estimate an approximation of the RR. This is called the odds ratio, referred to as OR. In the rest of this report, I will consider evidence obtained from both cohort studies and case-control studies, and I will refer to the findings of these studies as RRs, even if technically speaking, the results from case-control studies are ORs.

Bias, confounding, effect modification. The aim in an epidemiologic investigation of a putative risk factor is to derive an accurate estimate of the RR between exposure to the agent and the disease at issue. Because the investigator does not control the conditions in which people live and are exposed to different agents and their willingness to participate in research, there are many potential sources of distortion in epidemiologic research. While there are many sources of distortion, they can be bundled into a few large families of sources of distortion.

Bias refers to a systematic distortion in study findings, resulting from the way the study was designed or the way the data are collected. Specific examples of types of bias will be discussed below as they pertain to talc and ovarian cancer.

Confounding is sometimes considered to be a type of bias, and sometimes it is considered a type of distortion on its own. This is merely a semantic distinction. Confounding refers to the situation where the association under study between factor F and disease D is distorted because there is a third factor X which happens to be correlated with F and which is a cause of disease D. For instance if we want to study the association between occupational exposure to talc in mines (factor F) and lung cancer (disease D), we need to be mindful of whether cigarette smoking (factor X) is more common in talc miners than in the rest of the population. Confounding differs from other types of bias in that it depends on relationships among different variables in the population, rather than characteristics of the study design and data collection.

Effect modification refers to the phenomenon whereby a given factor has a different effect in one sub-population than in another. If we study the association between that factor and the disease in the entire population without distinguishing the two sub-populations, we might end up with an estimate of the association that does not convey accurately the association in either sub-population. For instance, if it were the case that a certain genetic characteristic G increases the risk of pre-menopausal ovarian cancer but has no impact on post-menopausal ovarian cancer, then a study of the association between G and ovarian cancer that does not discriminate by menopausal status, would find an RR result somewhere between the null value among post-menopausal women and the true RR value among pre-menopausal women. Depending on the proportions of pre- and post-menopausal women in the sample, the overall RR might be so close to the null, that we might erroneously conclude that there is no association at all. In this example, it might actually be quite simple to detect the effect modification, since age is always recorded and menopausal status is usually recorded and investigators are sensitized to the possible effect modification of female cancers by hormonal status. Other potential effect modifiers may not be so easily available and they might not be on the radar screens of investigators. Effect modification can in some unusual circumstances completely wipe out a true causal

association (as when the agent causes cancer in some people but prevents cancer in others!). But generally, if there is a causal effect of the agent in one stratum of the population and no association in another stratum, and if we fail to stratify the population according to the effect modifier, it will have the effect of producing an overall RR that is lower than it truly is in the sensitive stratum and higher than it truly is in the insensitive stratum.

Effect modification is closely related to and sometimes synonymous with interaction or synergism.

Publication bias refers to the tendency for some evidence never to “see the light of day”. Namely, when results are “negative” or “null”, it may be that investigators never bother to submit them for publication, or alternatively that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small.

In this section I have briefly outlined some potential sources of distortion of a typical epidemiologic study. I have done this in a high-level generic way. Below, after presenting results of my review of pertinent literature on powders and ovarian cancer I will return to commenting on the possible impact of such distortions in this body of literature.

Exposure variable and exposure metric

An **exposure variable** can be anything that can influence the occurrence or outcome of disease. The term is used for such disparate entities as external components of what we eat, drink, breathe, hear or see and microbiological organisms, chemicals or forms of radiation.

Depending on the nature of the variable, information on an exposure variable can often be ascertained from epidemiologic study participants by questioning them. This is the case for variables like cigarette smoking or use of talc powders. For some variables, like exposure to a virus or to specific air pollutants or occupational chemicals, it is usually necessary to invoke more intensive data collection methods to ascertain exposure.

An ***exposure metric*** signifies a way of defining a variable for statistical analysis. The simplest metric is a binary variable: exposed or unexposed. For most exposure variables, like exposure to talc powder, there can be a very wide range of degree of exposure. And it is pertinent to create more nuanced exposure metrics that take into account the degree of exposure that different people have experienced, metrics such as duration of exposure, intensity or frequency of exposure and even cumulative measures of exposure over long periods of time.

Measurement error. Whenever we are measuring a variable in an epidemiologic study, be it smoking, or weight, or socio-economic status, or blood pressure, or any other variable, it is virtually inevitable that there will be some degree of error in the measurement. There are ways of collecting data that make them more or less likely to involve error, but it is almost impossible to ensure that variables are measured with perfect validity and precision. Even such a variable as the diagnosis of ovarian cancer is subject to differences of opinion among pathologists and oncologists and the presence or absence and the histologic type of tumour is not a guaranteed 100% perfect diagnosis. The ascertainment of the lifetime history of talc exposure by means of an interview with a woman in middle age or later in life is certainly susceptible to the caprices of memory and the way the questions are formulated may influence the validity of respondents' reports of lifetime exposure patterns. It is likely that habits that were performed regularly are more reliably recalled than activities that were sporadic or that only occurred many decades earlier. Similar issues arise for all other variables collected in such studies. We refer to measurement error as random (or non-differential) if the degree of measurement error does not differ between cases and controls in case-control studies or between exposed and unexposed in cohort studies. As a general rule of thumb, it can be asserted that random (or non-differential) measurement error has a predictable distorting effect on the RR. Namely, while there are some rather obscure exceptions, non-differential measurement error tends to attenuate the RR towards the null value of 1.0, and the more measurement error, the greater the attenuation. A full explanation for why this is so is quite technical and can be found in advanced epidemiology textbooks, such as Rothman, Greenland and Lash 2008. A very simple explanation is that the presence of measurement error in assigning exposed vs

unexposed status leads to dilution of both the exposed group and the unexposed group. That is, the ostensible exposed group (i.e. the folks who will be labelled as exposed based on the study data collection) will contain some folks who are truly unexposed and the ostensible unexposed group will contain some folks who are truly exposed. If there really is a difference in risk between the true exposed group and the true unexposed group, this difference will be watered down by the inadvertent inclusion in each group of folks who are really in the opposite group. An analogy is the cross-contamination of two cans of paint. Suppose we have a can of pure white paint and a can of pure red paint. Suppose we have a way of quantifying the difference in color tone between the two paints. Then suppose we take some spoonfuls from the red can and pour them into the white can, and likewise take a few spoonfuls of the white paint and pour them into the red can. Now the color contrast between the two cans has been attenuated. The color contrast in this example is like the relative risk in an epidemiological study which has been attenuated because the exposed and unexposed groups have been cross-contaminated.

Dose-response. It is important not only to assess whether there is an association between a variable and a disease when the variable is defined in a binary (exposed vs unexposed) way, but also when the variable is defined in a quantitative or semi-quantitative way. When we analyse the risk as a function of the degree or duration or intensity of exposure, we refer to this as a dose-response (or exposure-response) analysis. The example of the smoking and lung cancer is instructive about the value of different metrics, though it cannot be assumed that all risk factors act the same way. Studies using the binary metric for smoking (smoker/non-smoker) have been very consistent and persuasive in demonstrating an association between smoking and lung cancer. Further, when data are collected and analysed regarding the degree of smoking, it becomes clear that there is a monotonic dose-response relationship. That is, the more smoking, the higher the risk. And the quantitative metric that manifests the strongest association with lung cancer is the cumulative amount smoked over the lifetime. This is perfectly logical. Since the cumulative exposure metric embodies information on duration and on intensity, it can hardly be less predictive of risk than either of the dimensions alone.

We cannot assume that there is a universal form of a dose-response relationship for every true causal relationship. Most commonly, in toxicology and epidemiology, the relationship between exposure and risk is monotonic; that is, as one increases, so does the other. This can include linear relationships (i.e. where a straight line on a graph describes the relationship) or exponential or many other curvilinear forms. It is also possible that there may be a threshold effect (the risk only becomes apparent after a certain level of effective exposure) or some other non-standard relationship.

Both the qualitative metrics (ever/never) and quantitative metrics (a lot of use compared with a little use) are valid and useful metrics.

Sample size refers to the number of participants in the study. As a generalization, large studies produce more statistically stable and precise estimates than small studies. In fact the stability of estimates or precision of estimates is not a simple function of the number of participants, or subjects, in a study. The precision of estimates depends, among other things, on the type of epidemiologic design.

In a case-control study the main determinants are the numbers of cases and controls and the prevalence of exposure in the two groups; in a cohort study the main determinants are the numbers of participants, prevalence of exposure, and the incidence of the disease of interest over the period of follow-up in the exposed and unexposed groups.

There is sometimes confusion about the notion of sample size when we compare cohort studies with case-control studies. The operational aspect of an epidemiologic study of cancer that most influences the precision of an estimate of RR is not the total number of participants; rather, it is the smaller number between the number of exposed cases of disease and the number of unexposed cases. In a typical prospective cohort study, one might need to enroll 100,000 participants in order to end up with a certain number of cases (say, 500 cases) of the disease of interest (e.g. ovarian cancer). In a case-control design we might only need to enroll around 500 cases and 1500 controls to achieve the same statistical power as would be achieved by a cohort study of 100,000. The formal justification for this assertion is quite mathematical, and has to do with the fact that a sample of a population can give very accurate estimates of the characteristics of an entire

population. Thus, the simple comparison of 100,000 participants in a cohort study and 2,000 participants in a case-control study is in no way a valid marker for the relative statistical power of the two hypothetical studies. There are admittedly other advantages and disadvantages of the cohort vs the case-control design, and reviewers should consider the various aspects before deciding on the relative weight to give to the results of the different studies. But it is definitely not appropriate to merely compare the numbers of participants as an indicator of study validity.

While precision is based on multiple factors and different ones in case-control and cohort studies, there is a parameter which embodies the different factors quite well, and which is common to both case-control and cohort studies, namely, the number of exposed cases. For this reason, in laying out the various study results below, in addition to the relative risk estimates and their confidence intervals, I will show the numbers of exposed cases.

While it may affect the precision of estimates of RR, the size of the study does not in itself systematically affect the estimates of RR. That is, it is not the case that small studies produce systematically exaggerated RR estimates or systematically low RR estimates. However small studies can produce more wildly divergent RR estimates than large ones, in either direction, towards the null or away from the null.

Meta-analysis and pooled analysis: There are two distinct ways that evidence from multiple studies can be combined to derive a new overall statistical summary or synthesis of those studies, a meta-analysis and a pooled analysis. A meta-analysis uses the published results from each study and averages those results using some optimal weighting procedures. In order to implement a meta-analysis it is necessary to find all relevant studies on a topic that have published results in a fairly standardized way. The statistical algorithms typically used to average the results from different studies also provide statistics that evaluate how heterogeneous are the results from the different studies. The interpretation of such heterogeneity statistics is not straightforward. If the results from different studies are homogeneous, it adds to the confidence in the meta-estimate. If they are heterogeneous, it may indicate that the association is really different in different populations, or that there are some methodological characteristics of the different studies

that have influenced the results in different ways. Unless a significant methodological flaw can be identified that has caused the heterogeneity, the best overall estimate remains the meta-estimate.

A pooled analysis is one in which the investigator gets access not only to the published results from different studies, but rather to the individual data of every person in the studies. The latter is harder to achieve because it requires high buy-in and input from the investigators of the original studies; a meta-analysis is much easier to organise. Because a pooled analysis allows for standardization in the definition of variables and statistical models, it can be a more powerful means of summarizing data than the original studies themselves.

Multifactorial etiology of disease. Chronic diseases such as cancer are multifactorial in two distinct ways. On the one hand, each case of disease results from the unfortunate conjuncture of a combination of factors (these might include for example, genetic predisposition, diet, environmental pollutant, occupational exposure, medical intervention, viral infection, lifestyle habits, etc.) which combine over a lifetime to initiate and promote development of the disease. In this sense, each of the factors that are part of the combination for that person was a necessary contributor to the disease process, although it was not sufficient on its own to provoke the disease. Despite the fact that none of the factors were sufficient to produce the disease on their own, each of the contributory factors may be considered to be a cause of the disease. The disease would not have arisen if any of the contributory factors had been absent. This is one meaning of the multifactorial etiology of disease.

The second meaning is that the combination of factors that induce cancer in one person may not be the same as the combination that induces cancer in another person. Indeed, at the population level, there may be many combinations of causal factors for the same disease. Some factors may be common to different combinations. For example, it may be that in one case of lung cancer, the combination of factors included genetics, exposure to air pollution, exposure to radon in the home, and smoking; while in another person, the

combination of factors included genetics, insufficient dietary consumption of anti-oxidants like carotene, exposure to asbestos, and smoking.

Some characteristics of carcinogens and epidemiologic research on cancer: The following characteristics of most known carcinogens provide a framework for some of the thinking behind the design and interpretation of epidemiologic studies of cancer.

- There is typically a long induction period between exposure to a carcinogen and appearance of the disease. Thus, if a study has not allowed for a sufficient passage of time between the exposure and the disease, the result may report that there is no risk, where in fact there is a risk, but insufficient time has elapsed to make the risk visible.
- There is variability in the carcinogenic potency of different carcinogenic agents; some induce much greater relative risks than others.
- For any given carcinogen, the degree of risk due to exposure generally increases as the exposure level increases, but the shape of the dose-response curve may differ from one carcinogen to another.
- Most known human carcinogens were first discovered as such either by means of astute observation of a clinician noticing a cluster of cases among people who shared a common characteristic (such as working in a particular workplace) or by means of epidemiological research. In most cases, there was no known mechanism to explain the association at the time. Where the mechanisms have been elucidated, they were usually discovered subsequent to the epidemiologic demonstration of a causal relationship. (Siemiatycki 2014)

4.2 *Bradford Hill “guidelines”*

Because of the complexities of epidemiologic research, there has been some concern with how epidemiologic evidence should be used to draw causal inferences. Various authors have written about the types of information that might be considered in assessing whether a body of evidence demonstrates a causal relationship. A set of guidelines, developed in the context of the Surgeon-General’s Report on Smoking and Health (1964) and authored by

Bradford Hill in 1965, has achieved a wide consensus in the epidemiologic community as a pedagogical guide. Hill himself referred to these guidelines as “aspects” or “features” or “characteristics” of an association, and warned against treating them as “hard-and-fast rules of evidence that must be obeyed”. (Hill, 1965) He deliberately avoided referring to them as “criteria.”

Since Hill wrote those thoughts at the beginning of the era of modern epidemiology, without the benefit of decades of practical experience in the way those thoughts were taken up, and how they applied to issues other than smoking and cancer, it is understandable that the practice of evaluation of causality has evolved. A first observation, often overlooked, is that Hill took as a starting point for his writings that chance had been considered as an explanation for the smoking-cancer association and determined to be unlikely. In the historic context of 1964-1965 and the debates around smoking and cancer, this was a reasonable assumption to make, but for any other putative associations, this must be considered. Over the years, respected authors have paraphrased and updated these aspects in various ways, and this will undoubtedly continue. For instance, leading textbooks of epidemiology as well as the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) all have different formulations of Hill’s guidelines.

In the light of 50 years of practical experience after these guidelines were written, and based on my practical experience of evaluating causality in many forums and on many topics, I would paraphrase (and modernize) Hill’s guidelines as follows:

Strength of the association: This can be measured by different parameters, but for cancer studies it is usually measured by the magnitude of the relative risk or odds ratio.

Statistical significance of the association: While this guideline was not explicitly listed by Hill, it is nonetheless in practice an implicit and distinct consideration in assessing causality. If the estimated RR is quite high, indicating a strong association, but is based on a very small study with low precision, this might be solely due to statistical variability. (For instance, when we flip a balanced coin 10 times, we do not always end up with 5 heads and 5 tails. Sometimes, by chance, we may end up with 6 heads and 4 tails. Does this prove that the coin was not balanced?) Evaluating the role of statistical chance as a possible

explanation of the observed association is important. As explained above, the absence of statistical significance is not strong evidence of an absence of a real relationship.

Dose-response relation: If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. There are some counter-examples however where the effect is only observed after a threshold of exposure has been crossed. There are various ways to assess whether there is a dose-response relation. Hill pointed out that the main challenge is to establish reliable and measurable quantification of exposure. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency).

Absence of bias: There are many forms of bias that can infiltrate an epidemiologic study. It enhances the likelihood of a true causal association if we can confidently exclude all the plausible sources of bias explanations for the observed findings. This guideline can also be considered as a component of a guideline to consider other possible explanations for the association.

Temporality: It is clear that the exposure should precede the outcome (i.e. the disease). To ascertain whether the cancer was a result of the exposure or the exposure occurred after the cancer onset seems like a simple thing, but sometimes it can be difficult to ascertain with certainty.

Cessation of exposure: It would add to the credibility of the association if it had been demonstrated that subjects who cease exposure to the agent experience reduced risks of disease compared with those who continue to be exposed. In practice this is an extremely difficult characteristic to demonstrate, partly because of the difficulty or even ethical impossibility of changing people's habits for scientific experimentation purposes. But occasionally there may be a "natural experiment" wherein large numbers of people cease their exposure and the effects can subsequently be measured in an epidemiologic fashion.

Specificity of the association: It was believed that individual risk factors have specific pathological effects, and Hill posited that if we observe that a given agent is associated with

many different pathologies, it increases the likelihood that these are somehow spurious observations, resting on some type of bias in the studies of that agent. In reality, this Hill characteristic has fallen out of usage in the intervening years with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

Consistency of findings between studies (or replication of findings): Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship.

Coherence with other types of evidence: In the case of tobacco and cancer, it was seen that the historic trend in lung cancer mortality rates in the US and UK followed quite closely the national trends in consumption of tobacco, with a 20 year lag. This was interpreted by Hill as corroboration of the results observed in case-control and cohort studies. Epidemiologic evidence of coherence could conceivably take many forms, and the opportunity to assess coherence is something that is specific to the factor under investigation. Assessment of coherence with historic mortality trends would only be possible in the case of a factor whose exposure in the population changed quite dramatically over time in a way that can be documented, and for which the attributable fraction of the disease due to that factor is very high. This was the “perfect storm” of circumstances that allowed for an assessment of the tobacco-lung cancer association by means of time trend correlations.

Analogy: Hill reasoned that if a factor is somehow similar to another factor that has already been shown to be a risk factor for the disease, then it increases the plausibility of a similar impact due to that putative factor. This is such a vague guideline, with no clear implementation suggestions, that it is not often referred to and rarely implemented.

Biologic plausibility: This guideline can encompass many dimensions of information, including physiology (can the agent or its metabolites reach the organ?), animal carcinogenesis (does the agent produce tumours in experimental animals?), cell studies that reveal mechanistic data, and other biologic information on the toxicology of the agent.

Implementing Hill's guidelines: As Hill himself insisted, sophisticated users of these guidelines do not use them as a formal checklist. He summarized his views as follows:

« What I do not believe ... is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? »

The authors of the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) clearly stated that Hill's guidelines are not formal criteria, but rather are more in the nature of a memory aid to help us review the evidence about any given causal association. They stated it this way: "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines."

I have served on many panels to review evidence of causality on one topic or another, including on several IARC Monograph panels that reviewed evidence of carcinogenicity. The IARC process, like the others I have participated in, does not use the Hill guidelines in any rigid formal way. The ideas embodied in Hill's guidelines permeate our thinking about how to evaluate causality, but the operationalization of these guidelines is specific to the problem and to the expert making these determinations. Thus any suggestion that Hill's "aspects" or "features" or "characteristics" of an association should be used as a formal checklist of criteria is simplistic and wrong. To do so would contradict the opinions of experienced epidemiologists, the Manual on Scientific Evidence, and Bradford Hill himself.

In this section, I have laid out and explained the Bradford Hill guidelines in a generic way. Below, in section 8, I will consider how these apply in the context of the talcum powder – ovarian cancer issue.

5. Epidemiologic evidence regarding talc and ovarian cancer

Following some reports in the early 1980's that raised questions about a possible link between use of cosmetic talc powder by women and the risk of ovarian cancer, there were several epidemiologic studies on the topic. By the early 2000's the issue was garnering some attention in the scientific community. The International Agency for Research on Cancer, the premier agency for evaluation of carcinogens, decided to conduct a review of the issue in 2006. Following that review, there have been further studies conducted on the topic.

In the context of a legal action, my mandate is to review all relevant scientific evidence available to date, in order to provide the court with my opinion regarding the link between talc powder exposure and ovarian cancer. The methodology I employed is the same one I have used in my career as an internationally recognized researcher.

5.1 IARC review and evaluation of talcum powder products

As mentioned above in Section 2, the International Agency for Research on Cancer (IARC) is the premier institution in the world for cancer epidemiology and for environment and cancer research. One of its mandates is the evaluation of the carcinogenicity of different agents with which humans come into contact, and this mandate is carried out by the Monograph Programme of IARC. This is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens.

In February 2006, there was such an IARC Monograph meeting to evaluate some agents, including talc. The IARC Working Group comprised 16 highly respected and recognized scientists from around the world; I was asked to Chair the Working Group. We reviewed all

the evidence that was available up to that point in time. This certainly included epidemiologic evidence, but it also included evidence from experimental toxicology, physiology, molecular biology and other domains. The IARC Monograph programme has a formal system for classifying agents. The Working Group must classify an agent into one of the following categories:

- 1 Carcinogen
- 2A Probable carcinogen
- 2B Possible carcinogen
- 3 Not classifiable
- 4 Not carcinogen

After reviewing the evidence, the panel concluded that talc was a “possible carcinogen”, based primarily on evidence regarding the association between dusting powders and ovarian cancer. Here is the definition of this category from the IARC Monograph:

“Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals.”

This 2B categorization was based on the panel’s decision that there was “limited evidence of carcinogenicity in humans”, which is in turn defined by IARC as follows:

“Limited evidence of carcinogenicity in humans: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.”

Subsequent to the completion of the IARC Monograph on talc, a subgroup of the epidemiologists who were on the IARC Working Group, including myself, reviewed the evidence again, but with a view to producing a meta-analysis of the results from the most informative studies conducted to that time. This resulted in the paper by Langseth et al. (2008). This paper was not an IARC publication.

5.2 Information consulted for the present review

In preparation for formulating my current opinions on this topic I assessed, researched, reviewed and consulted a large number of documents, including, but not limited to: all original epidemiological studies published on this topic, all meta-analyses and opinion pieces, experimental toxicology, molecular biology, mechanistic studies, and the IARC Monograph on talc which reviewed all informative studies that had been published before 2006. I was given access to and also reviewed the various expert reports and depositions that have been submitted in various talc cases, either on behalf of the Plaintiff or Defendant, and various internal company documents obtained in discovery.

I systematically reviewed the lists of references of all relevant studies referenced in the IARC report as well as in various meta-analyses and in all recent articles on the topic to identify yet more relevant publications on talc and cancer.

Because some studies have been published in multiple papers and because some papers have included reports on multiple studies, there is not a one-to-one relationship between studies and published papers.

Additionally, I considered evidence regarding the toxicology of talc by reviewing the toxicology evaluation conducted by the IARC Working Group, the summary of talc's putative toxicology referenced in various scientific publications, and the expert reports of various scientific/medical experts in this case.

The central focus of my review is on the epidemiologic evidence.

A complete listing of the documents I consulted, as well as references cited explicitly in this report, is provided in the Bibliography. The Bibliography is in two Parts; Part A comprises all the publications and reports that can be found in publicly available scientific literature. Part B comprises company documents or documents from reports or testimonies of experts.

5.3 My methodology for this review

Table 1 lists the steps I undertook to accomplish my mandate.

5.3.1 Selecting studies for review

To aid in the present assessment of whether or not there is a causal relationship between talcum powder exposure and ovarian cancer, I carried out an up-to-date review of the scientific literature, primarily the epidemiologic literature, concerning the association between use of talc powder and risk of ovarian cancer. This involved meta-analyses to estimate the effect of having ever used perineal powdering, and an assessment of evidence regarding dose-response.

The first task was to find the relevant publications and to set out the distinct pieces of epidemiologic evidence, namely the results of different studies. Based on a number of reviews on the topic of talc and ovarian cancer, including the IARC report, I systematically went through the reference lists to identify all publications that seemed to contain results on the topic. I further conducted a Pubmed search and this did not produce any new informative publications that had not already been identified. In preparation of the meta-analysis, I eliminated from consideration papers that were outside the bounds of what a meta-analysis should contain (i.e. eliminate review articles, commentaries, meta-analyses, and articles that do not really pertain to the issue of perineal talc and ovarian cancer). From the 40 publications that remained, namely those that contained original results on the association between powdering and ovarian cancer, I extracted all results showing RRs between talc powdering and ovarian cancer, and I had these results put into a Filemaker database. This was a value-free exercise. I made no judgement at that stage about relevance or quality of the study or the published results. It was only an attempt to lay out in one “place” the whole of the evidence and to prepare for subsequent analyses. There were over 730 results in this database. On average each publication contained about 18 different RR results of various aspects of talc powder exposure and various types of ovarian cancer. Some contained fewer and some contained many more. (For instance, one study publication contained 180 results, with varying types of ovarian cancer and varying definitions of exposure to powdering.)

In deciding which results to include in a meta-analysis I had to respect the following principles:

- The results have to pertain to the issue of risk of ovarian cancer in relation to use of talc-based powders.
- Where there are sufficient numbers of results to support meta-analyses, there can be meta-analyses for different types of ovarian cancer, and for different routes of exposure to talc-powders.
- In each meta-analysis, each study should only provide one result, so as to avoid double-counting evidence.
- The decision about inclusion of a study should in no way be influenced by whether or not a particular study demonstrated high risks or low risks.

While these seem like simple principles to respect, there were complicating features of the scientific literature:

- Some studies were reported in multiple publications, sometimes the same study subjects were analysed and reported in different ways and sometimes different subsets of the study population were included in different publications. Sometimes the authors fail to clearly enunciate how the data used in one of their papers overlaps with data used in another of their papers from the same study.
- Different studies used different questions about powder use in their questionnaires, and sometimes the same study reported results by different ways of asking about or defining exposure.
- A given study may have presented one result or many results, each addressing a different definition of the talc exposure variable and different way of grouping the ovarian cancer cases.
- Different studies dealt differently with the histologic sub-types of ovarian cancer, sometimes grouping them all, or sometimes separating them, or sometimes reporting both grouped and separate results for different sub-types.

- Different studies used different metrics for analysing powder exposure and estimating its corresponding RR.
- Different studies dealt differently with the challenge of adjusting powder-related risks for possible confounding by other factors.

Decisions had to be made regarding which types of exposure to consider, which types of ovarian cancer to consider, which metrics of exposure to consider and which studies and publications to consider. It is necessary to be rigorous in making such decisions ahead of time, rather than “cherry-picking” results from different studies that appear to support one theory or another.

Appendix Table A1 provides a list of those 40 publicly available publications that have included some original results that might pertain to the association between powdering and ovarian cancer. **Appendix Table A1** shows which publications were included and which papers were excluded from my meta-analyses. For each of the 14 excluded papers, the table also shows the reason. Some papers were excluded because the results did not pertain to ovarian cancer and powdering in the perineal region. Some papers were excluded because the results presented therein were subsumed by a subsequent publication by the same research team or as part of a pooled analysis of multiple studies. Notwithstanding my intention to identify all unique studies and to extract a best “bottom line” result from each study, the nature of the studies and how they were analysed and reported led to many judgement calls. It must be acknowledged that there can be differences of opinion among equally competent and equally well-motivated scientists in how to choose among the different publications and the different results within publications.

Fortuitously, and unbeknownst to me at the time, two other sets of investigators (Berge et al 2018; Penninkilampi et al 2018) carried out separate meta-analyses on this topic at about the same time as I was carrying out mine, and this gives an opportunity to do some cross-comparison of different reviews and meta-analyses. I will comment on these after presenting the results of my meta-analyses.

5.3.2 What were women exposed to in body powders?

Talc has been the main ingredient of body powders used by women over the past century. “Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibers ... Talc may also form as true mineral fibers that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a ‘habit’. Asbestiform talc fibers are very long and thin.”(IARC 2010) The structure of platy talc is characterized by a hexagonal sheet arrangement of silicon-oxygen tetrahedral groups in a common plane which creates a double-sheeted structure. These sheets are easily separated which accounts for the “silky” or “smooth” feel of talcum powder products (IARC, 2010). As a mined mineral, the precise chemical and physical characteristics of talc are in part determined by the particular geological formations from which it is extracted. The local conditions can also produce “impurities” in the extracted talc including asbestos, quartz and various metals. It is claimed that cosmetic talcum powder products normally contain >98% talc (Zazenski *et al.*, 1995) but the purity may have been lower in the past. (IARC 2010) When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained in those products.

Asbestos is a commercial term that comprises six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite. Similarly to talc, these six minerals can occur in a non-asbestiform habit. Some types of asbestos are found in the same geological formations as talc.(IARC 2010)

By the 1970’s it was reported that asbestos fibers were found in commercial talcum powder (Cralley 1968; Rohl 1976), though there was some doubt expressed regarding the quantification of the exposure and the ability to discriminate between asbestiform and non-asbestiform talc. (Krause 1977; IARC 2010) The talc industry was constrained to remove asbestos from talcum powder products. Representatives of the industry have claimed that talcum powders were free of asbestos fibers since the 1980’s (Hopkins 2018; Pier 2018), but this assertion has increasingly come under doubt as number of labs have

reported finding asbestos fibers in talcum powder products. (Blount 1991; Paoletti 1984; Gordon 2014; Longo et al 2017; Longo et al 2018; Blount deposition 2018; Pier deposition 2018) These various studies that have reported finding asbestos in historic talcum powder samples have been challenged by other reports that failed to find meaningful amounts of asbestos in historic talcum powder samples. (CIR 2013; Anderson 2017) These various findings and opinions are somewhat complicated by the fact that both talc and asbestos have varied chemical and physical characteristics and various methods can be used to measure them.

What is clear is that asbestos, and all forms thereof, has been evaluated to be carcinogenic. It has long been recognized that inhalation of asbestos carries with it a risk of lung cancer and of mesothelioma, a cancer of the lining of the lungs, as well as larynx cancer. What has only recently been recognized is that women who are exposed to asbestos experience an excess risk of ovarian cancer. (Straif 2009; IARC 2012) This conclusion was based on five studies; a subsequent meta-analysis reported that the RR of ovarian cancer among asbestos-exposed women was a highly statistically significant 1.77 (1.37-2.28). (Camargo 2011) The route of exposure that generates risk of ovarian cancer among women exposed to asbestos is not clear, but inhalation and migration of asbestos particles to the ovaries has been proposed as a credible biologically plausible mechanism. (Miserocchi 2008)

Among the metals detected in talcum powder products are some which are recognized carcinogens, namely nickel and chromium. It is not known how widespread was the “contamination” of talcum powder products by these metals and how high were the concentrations in the entire commercial production of talcum powder products of the past several decades, and how these exposures measure up to exposures that may cause cancer. However, evidence that asbestos and some other known carcinogens have been detected in some commercial cosmetic talcum powder products and credible mechanisms that such particles can translocate to the ovaries is an important consideration in deriving an opinion on biological plausibility, and I will consider it below in my section on biological plausibility of a causal link between talcum powder products and ovarian cancer.

Alternative formulations of baby powder include cornstarch formulations, which have become available in the past 30 years. It was possible for women to purchase and use cornstarch products or talcum powder products. Most epidemiological studies have not tried to ascertain whether the women in their studies used talc-based or cornstarch-based formulations and many women may have been unaware of the composition of the powders they used at different times. It is impossible to ascertain with certainty from most of the publications whether the reported epidemiologic results pertain to talc-based powders or cornstarch-based powders or both. Those studies that did report results for cornstarch had few women self-reporting use of cornstarch and the risk estimates were rather imprecise and unstable. For those studies that did report separately the findings for talc-based and cornstarch-based formulations, I used the results for talc-based powders. For those that did not make such distinction, I used the results combining all types of powders as reported. If it turns out that there is an increased risk associated with talc but not with cornstarch, the inability to discriminate the two in statistical analyses would have the effect of diluting the estimates of risk due to talc. That is, the RR estimates would be attenuated.

5.3.3 Routes of exposure

Some studies reported results based on particular ways of using the powders, such as on feet or perineal use or use after bathing or use on sanitary napkins or use on diaphragms or use by male partners, and so on. And many studies just reported results for all routes of perineal exposure combined. For my Main analyses, I aimed to use the reported results pertaining to all types of perineal use combined. Where the results were reported for individual routes of exposure rather than all perineal use combined, I identified the one that came closest to powdering in the perineal area from all routes.

The number of studies providing results pertaining to any of those specific routes of exposure was much less than the number providing evidence for all routes combined and insufficient to provide reliable meta-analysis results for route-specific estimates of RR. Among the route-specific reports, the one that had most often reported RR results was exposure from dusting of sanitary napkins. I will conduct a separate meta-analysis regarding the risk of ovarian cancer in relation to use of powder on sanitary napkins.

5.3.4 Questionnaire items on use of talc powders

In the case of exposure to cosmetic talc powder, the most common and realistic way of ascertaining exposure has been to question women. But there are many ways this can be done, and indeed many types of questionnaires have been used. A very simple format that has been used is to ask a question such as “have you ever used powders in your genital area?” But, the validity of the response would be enhanced if the question is framed in a more specific manner, so long as the respondent can be expected to know the answer to the more specific question. One possibility would be: “have you ever used powders that contained talc on your genital area more than once a week for at least 6 months of your life? This would include powdering your genital area directly or powdering your underwear or powdering your diaphragm or powdering your sanitary napkin.” There are scores of ways such questions can be asked, and there has been variability in the methods of questioning among the different studies of powder use and ovarian cancer. In most studies, the questionnaire question about Ever Use was actually about Ever Regular Use, not Ever Occasional Use.

Among women who used powders, there can be an enormous range of usage from a few occasions in a lifetime to profuse daily usage. Among the many dimensions of talcum powder exposure that might influence the risk of cancer are the following: manner in which the talc was applied, age at which exposure began; if it ended, age at which it ended and years since it ended, frequency of use per day, week or per month, multiple applications including to genitals, undergarments, sanitary napkins, etc., and whether and how that varied at different ages. Some studies have used a single simple question, while others have used scores of questions to get at the lifetime history and many facets of powder use.

While I believe there are quality differences between the different studies in the way talc powder data have been collected, I have refrained from imposing my judgement about the quality of the questionnaire data on the selection of studies to include in meta-analyses.

5.3.5 Metrics of exposure

I used the reported results for the binary metric Ever Regular Use vs Never Regular Use, given the limitations of the available data, and using the investigators' decisions about how best to measure this. While this may seem like a simple tactic to implement, some studies were reported in such a way that in fact I had to make "judgement calls" about which of the reported results came closest to the desired metric.

For "dose-response" assessment, I used three pertinent metrics of exposure: duration (years), intensity/frequency (uses per day, week or per month), and cumulative number of applications, measured sometimes in absolute numbers or sometimes in quantiles. Of the three, the most meaningful is the cumulative number of applications.

6. My meta-analyses regarding talcum powder products and ovarian cancer: data included and results

6.1 Features of the studies

Following the exclusions indicated in Appendix Table A1, **Appendix Table A2** shows the studies that ended up being included in one or more of my meta-analyses, and brief descriptions of administrative and contextual features of each study. **Appendix Table A3** shows, for the same studies, some information about the talcum powder exposure variable and the covariates used by the authors in their control for confounding.

Appendix Table A2 shows that most studies were conducted in the USA. All but three were case-control studies and of the case-control studies, all but four used some type of population control series. Most studies had fieldwork data collection in the 1970's and 1980's; only a few studies started data collection after 2000. Table 3 shows for each study what exposure variable I was able to use to approach the notion of Ever exposed regularly to talc powder in the perineal region. Different studies had different questions in the questionnaire and different studies reported different variables. The questionnaires usually elicited lifetime use that was more than very sporadic, with terms like "regular" use. Only the Gonzalez 2016 study failed to ask about lifetime exposure before the interview; they asked about usage only in the preceding 12 months. The Gates 2010 study

asked about use of talc up to 1982 but not afterwards. Some studies asked separately about different routes of exposure and then rolled them together in statistical analyses, while some rolled all routes of exposure together in their questioning. The term that I show in Appendix Table A3 is the term that the authors reported in their publication of results; it is sometimes rather cryptic. Appendix Table A3 also shows which variables that the authors reported having used as adjustment variables. Sometimes these are variables that were explicitly included in final statistical models, and sometimes these were dealt with in a more indirect way such as a staged analysis in which a screening is conducted using a change-in-estimate procedure.

All meta-analyses were conducted using the well-known package Comprehensive Meta-Analysis Version 3. (Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013; <https://www.meta-analysis.com/index.php?cart=BFZW2135997>)

6.2 Association between binary variable talc powdering and all types of ovarian cancer combined – data and results

6.2.1 Individual studies and results on binary exposure variable

Table 2 shows RR results, as well as the corresponding 95% confidence intervals, for each informative study included in the Main meta-analysis or in any sensitivity analyses. (I will explain this distinction below.) As I explained in Section 4.1, the single number which reflects quite well the statistical strength of a study, be it case-control or cohort, is the number of exposed cases, and I have included this parameter in Table 2. Table 2 shows the RR reported in each study by Ever (regular) use of powder in the perineal region (all routes of perineal exposure including direct powdering on genital area, on sanitary napkins, on underwear and on diaphragms). The table shows results for all types of ovarian cancer combined.

Before conducting any meta-analyses, we can peruse the results in Table 2 to observe certain patterns.

Of the 33 RR results shown in Table 2, two are below 1.0, one equals 1.0, and 30 are greater than 1.0. On the null hypothesis that there is no true association between powdering with

talc and ovarian cancer, we would expect as many of the RR estimates to be above 1.0 as to be below 1.0. The observed distribution (2 below and 30 above) is clearly and strongly in defiance of the null hypothesis. Further if we rank the RR estimates from lowest to highest, the median value, the one in the middle, would be 1.34.

This informal analysis does not take into account that the 33 estimates in Table 2 are not strictly independent of each other. There are various ways to carve out independent sets of results from this list of results in Table 2, and the meta-analyses will be designed to do that. But no matter how the studies are configured, it will be found that one or two of the RR estimates are below 1.0 and somewhere between 20 and 26 are above 1.0. Such an imbalance cannot be due to chance.

6.2.2 Strategy for Main analysis and sensitivity analyses

An investigator typically has in mind a strategy for analysing and presenting the results. There may be some judgement or assumptions involved in deciding on the strategy. The investigator may wish to see how the results would be affected if other judgements or assumptions were made. In other words, how robust are the results to alternative judgements and assumptions. Such alternative analyses are referred to as *sensitivity analyses*.

There were several dilemmas in selection of studies and results to include in the meta-analysis. I made decisions in each case that I believe provides the best basis for a meta-analysis. But in deference to other possible decisions that might have been made, I conducted some sensitivity analyses as well. I list what the dilemmas were and which options were selected for Main analyses and for sensitivity analyses.

a. Terry 2013 and Wu 2015. The Terry 2013 paper brought together data from 8 different research teams. Some of those teams had previously published their results on talc and ovarian cancer and some had not. Normally, a pooled analysis would take precedence over the individual component studies. In this case, however, there were complicating factors. The Los Angeles component study of Terry 2013 (Wu, Pike and colleagues) was conducted in stages and the Terry 2013 pooled analysis only had access to the early stage. Subsequently, Wu and colleagues carried on with their data collection, and published a

more complete set of results from their study in Wu 2015. The Terry 2013 paper contained 208 exposed cases from the Los Angeles study, whereas the Wu 2015 paper contained 701 exposed cases. In the entire Terry 2013 paper there were 2600 exposed cases. Ideally, we would wish to exclude from the 2600 exposed cases in the Terry 2013 paper, the 208 exposed cases that came from the early Los Angeles data. But that information was not available. Thus there is an 8% overlap between the exposed cases in the Terry 2013 paper and those in the Wu 2015 paper.

I adopted the following strategy. For the Main analysis, I included both Terry 2013 and Wu 2015. The 8% overlap of exposed cases is unfortunate but I believe its impact would be trivial, and in any case we will have some empirical evidence of its impact from a sensitivity analysis.

I conducted sensitivity analyses using a different strategy. The Terry 2013 paper contained a table in which the individual results of the 8 component studies were reported. I used the results as reported there for 6 of the 8 component studies, for which the Terry paper contained the latest results. For the Los Angeles study I used the result reported in Wu 2015 which was much more complete than the L.A. study result in Terry 2013. The eighth study was the study of Cramer that was one of the components of Terry 2013 but that was also reported subsequently in Cramer 2016. It is not clear whether the Cramer 2016 paper contains more up to date data than the corresponding component in Terry 2013, but it possibly does.

To summarize, the Main analysis contained pooled result from Terry 2013 and the result from Wu 2015. There were sensitivity analyses that dropped the pooled result from Terry 2013, but included the (apparent) latest published result for each of the 8 components.

b. Nurses Health Study. This cohort study was initiated in 1976 and was not a study of talcum powder products and ovarian cancer. The study involved a wide-ranging annual questionnaire which inquired about many health related issues. In 1982 there was a very succinct question about use of body powders. The cohort has been followed-up to ascertain the occurrence of cancers (or other diseases). There was a publication that contained results on talc and ovarian cancer from this study in 2000 (Gertig 2000); later, after more

years of follow-up there were two further papers presenting results on talc and ovarian cancer (Gates 2008 and Gates 2010). Clearly the Gertig result did not belong in my meta-analysis, since it was subsumed by subsequent analyses, but the choice between the Gates 2008 and Gates 2010 was not so obvious. Gates 2008 was based on a nested analysis of a subset of the cohort that probably entailed better control for confounding. Gates 2010 was based on the entire cohort and thus on a much larger sample size. The two RR estimates from the Gates papers are quite different from one another (RR=1.24 in Gates 2008 and RR=1.06 in Gates 2010). It is not clear whether the difference in results is due to the different design and analytic procedures used in the two papers. The authors did not comment on the inconsistent results.

My Main analysis included Gates 2010 but not Gates 2008. Some sensitivity analyses contained Gates 2008, but not Gates 2010.

It should be noted that whereas I did not use the Gertig paper results in the meta-analysis of Ever / Never Use of talcum powder products, I did use some dose-response results from Gertig because subsequent publications from the Nurses' Health Study did not present such results.

c. Schildkraut (2016). This was a case-control study of ovarian cancer among African American women. The fieldwork and interviewing was carried out from 2010 to 2015. The authors speculated that publicity surrounding two class action lawsuits on talc and ovarian cancer in 2014 may have subsequently induced bias in the validity of reporting of talc exposure. Consequently, in their analysis and report, they presented two sets of results, one for all women in the study, and another for those interviewed before 2014. It is impossible for me to evaluate the validity of the speculation, as it was for the authors. Consequently I will use the results from the entire sample and those from the pre-2014 sample. I refer to the entire Schildkraut study result as Schildkraut A and the pre-publicity result as Schildkraut B.

The Main analysis contained Schildkraut A. Some sensitivity analyses contained Schildkraut B.

d. Shushan (1996). This ovarian cancer case-control study, conducted in Israel, reported results on talc and ovarian cancer, but the report was quite cryptic regarding the data collection and the talc exposure variable.

The Main analysis excluded Shushan 1996. Some sensitivity analyses included Shushan 1996.

6.2.3 Results of meta-analyses on binary exposure variable for all ovarian cancers

Figure 1 shows the printout from the Comprehensive Meta-analysis (CMA) package for the Main meta-analysis for the association between ever regular use of talc powder in the genital area and all types of ovarian cancer combined. 21 RR results were used in the Main meta-analysis, but the Terry 2013 study represents 8 different study teams and 10 distinct studies. In the forest plot, I have ordered the studies in increasing magnitude of the RR estimate. It can be seen that only one study produced an RR estimate to the left of the null value of 1.0, while 19 studies produced an RR estimate to the right of the null value of 1.0.

The meta-estimate of RR is 1.28 with a 95% confidence limit from 1.19 to 1.38. The p-value is too small to register in 2 digits. This is a very highly statistically significant result. The probability of this result being attributable to chance is vanishingly small.

The 21 RR estimates in this Main meta-analysis had a fairly low p-value for heterogeneity, 0.07, but it was not statistically significant. This means that there was considerable variation in RR results across the studies, but this might have been due to chance. That there is significant variation in RR estimates is not surprising. The different studies were conducted among different populations, using different methodologies. It would be surprising if there was no variation. It is nevertheless true that in the current state of knowledge the best estimate of RR is the meta-estimate of 1.28.

Table 3 shows the results of the Main meta-analysis again and contrasts it with the results of seven sensitivity analyses that embody alternative plausible strategies for selecting studies and selecting results within studies. These alternative strategies had almost no effect. The meta-estimates of RR varied in a narrow range from 1.26 to 1.30. Even the lowest of these would lead to the conclusion that there is a highly significant association.

It can be affirmed, quite confidently, that the apparent overall elevated risk for women who had ever used such powders is not an artefact of chance variation. This conclusion is not new. It has been stated by the authors of previous meta-analyses. However, I believe this conclusion is based on the most current and reliable data now available.

From a statistical point of view, each of the studies listed in Table 2, except for one or two outliers, shows a 95% confidence interval that overlaps substantially with the confidence interval of the meta-RR estimate (1.19 – 1.38). Further, the majority of the study-specific confidence intervals (including 2 of the 3 cohort studies) include the overall meta RR of 1.28. This shows that there are few if any studies that are not compatible with the overall RR estimate.

6.2.4 Other contemporaneous meta-analyses on binary exposure variable for all ovarian cancers

I started to conduct my meta-analyses in 2015 and revised it in 2018. Towards the end of my analyses, I discovered that two other teams of researchers were carrying out meta-analyses on the same topic at almost the same time. The simultaneous and independent conduct of these three meta-analyses provides a unique opportunity to cross-validate the methodologies and results. (I knew nothing about the two others and I assume they did not know either about mine or the other meta-analysis.) It is sometimes portrayed that meta-analysis is a fairly automated procedure which should produce identical results irrespective of who carries it out. This is far from true.

Even before the statistical part of the meta-analysis is conducted, the author of a meta-analysis has to assemble all of the relevant data. That usually consists of two steps: identifying all informative studies on the topic and identifying the relevant result from each study to include in the meta-analysis. There are many ways to do these steps, and it is not surprising that different, equally competent, investigators may make different decisions about how to identify the studies and how to identify the most relevant results. This is particularly true in the area of observational epidemiology research, as opposed to clinical trials research. Research designs and methods of conduct and reporting are much more standardized in clinical trials research than they are in observational epidemiology. In the

area of research on talc and ovarian cancer (which is observational) there are many opportunities for judgement of the author of the meta-analysis to come into play, and in section 5.3.1 I have listed some of the decisions that I made, in the way I managed the selection of studies.

The two other meta-analyses were conducted by Berge et al (2018) and by Penninkilampi et al (2018). They conducted rather different search procedures than I did. Since I had already participated in the IARC review and the Langseth 2008 paper, I already had a head start on collecting the relevant scientific literature. **Appendix B** shows a 3-way comparison of the studies that were included in the meta-analyses by the three authors, and the data from each study that were judged to be most relevant by each author.

As a generalization, it can be seen that the three synchronous meta-analyses identified more or less the same studies and that in general they extracted the same result from each study; but this was not always the case. For my own meta-analysis, I was comforted to note that there was no study that was identified by one of the other meta-analyses that I had missed in my search of the literature (Appendix Table A1).

One of the main points of discordance in procedure was how the three analyses dealt with the Terry 2013 study. Namely, in my Main analysis I used the result of the pooled Ever/Never RR that was quoted by the Terry study, and dropped from consideration the various component studies of the Terry analysis. By contrast, the two others (Berge and Penninkilampi) adopted the strategy of using the results of the individual component studies rather than the overall pooled result. Berge 2018 used the results of the individual component studies as reported by Terry 2013, for most component studies, but for two component studies they used results that were reported in publications that gave results with additional cases. Penninkilampi 2018 also used individual component study results rather than the Terry 2013 pooled result. There are trade-offs between these different approaches. I prefer to use the Terry 2013 pooled result for two reasons. First, a pooled analysis with a standard set of covariates and a standard statistical model is considered superior to a meta-analysis of the components study results. Second, each publication tends to show a variety of results, and the author of the meta-analysis has to choose a

“best” one to represent the “bottom line” from each study. In the Terry pooled analysis, it was the investigators of the original studies, who were also co-authors of the pooled analysis, who chose which would be the “best” result to represent the study, and this in my opinion is more reliable than outside authors making that decision.

Table 4 shows the meta-RR results from each of the three meta-analyses. Notwithstanding the differences in choices and strategies of the three meta-analyses, the meta-RR results are quite similar, ranging from 1.22 (1.13 – 1.30) in the Berge analysis, to 1.28 (1.19 – 1.38) in my analysis, to 1.31 (1.24-1.39) in the Penninkilampi analysis. These three sets of results are really quite close to each other.

The methodology I used is sound and reliable and consistent with the high standards of my discipline. The strategy and decisions I made in relation to the studies selected and the data abstracted from each informative study is consistent with that methodology I use in my professional practice, and that has earned me recognitions and honors throughout the world.

The results shown in Table 4, are in the same “ballpark” as the meta-analysis previously conducted by Langseth 2008 and they are based on a larger pool of accumulated publications. This indicates that recent evidence is consistent with older evidence and reinforces the consistency of the evidence.

6.2.5 Meta-analysis on powdering of sanitary napkins

Tables 2-4 pertain to RRs for the combination of all routes of exposure to the perineum, including direct dusting and dusting on sanitary napkins, diaphragms, underwear, and condoms. When such an exposure variable was not provided in the paper, I used the one that came closest, with priority to dusting on the body directly. Most studies did not report RR results for every route of exposure separately. For the studies that did so, the numbers exposed were much lower than for all routes combined and there was limited statistical power in those analyses. Of the different routes, the dusting on sanitary napkins was generally the most commonly reported route apart from direct dusting. Consequently I assembled the data pertaining to dusting on sanitary napkins and conducted a meta-analysis of those results.

Table 5 shows both the individual studies that had results on sanitary napkin dusting and the meta-analysis result for those studies. The meta-RR was 1.08 (95%CI 0.89 - 1.31), heterogeneity $p=0.09$. Given the overlap between the confidence intervals between this meta-RR estimate for sanitary napkin powdering and the meta-RR for powdering the perineal area via any route (1.28; 95%CI 1.19 - 1.38), it cannot be affirmed that the result for sanitary napkins is statistically significantly lower than the meta-RR results in Table 3 for all routes of exposure; but the tendency is in that direction.

Berge 2018 and Penninkilampi 2018 also meta-analysed the data on use of powder on sanitary napkins. By contrast with my results, Berge 2018 reported an RR of 1.00 (95% CI 0.84-1.16) and Penninkilampi 2018 reported an RR of 1.15 (95% CI 0.94-1.41). Since their publications do not make it clear which studies and which results were used in these analyses, I cannot see easily what explains the discordance among the three meta-analyses for sanitary napkins powdering. In any case, it certainly appears that the RR was lower for application to sanitary napkins than it was for general perineal application. The interpretation of this finding is not self-evident. The different routes of exposure may entail very different frequency of exposure. For instance, whereas use of powders on sanitary napkins might involve exposure on only a few days per month, regular use on the perineal region often involves daily or near daily application. I am unaware of any evidence that would address the question of whether regular use on sanitary napkins leads to greater or lesser delivery of talc particles to the portal to the ovary than does regular powdering on the perineal region.

In any case, irrespective of the evidence regarding sanitary napkin exposure, the results in Tables 2 and 3 clearly show an association between exposure to talc in the perineal region and risk of ovarian cancer.

6.3 Dose-response – cumulative exposure, duration and frequency

An important part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern. Tables 6 to 8 show results for various quantitative metrics of exposure.

Trends by cumulative exposure: **Table 6** shows results from five publications that presented results based on a cumulative amount metric. Four of the studies were based on counts of numbers of powderings, while the Cook 1997 result was based on counts of the number of days on which powdering occurred. As can be seen by perusing the column of numbers of exposed cases, the Terry 2013 results dwarf the others in terms of the statistical information they contain. The Schildkraut study, with about one-tenth as many subjects as the Terry study, nevertheless has as many subjects as the other three studies combined. The relative statistical power of the different studies is also manifested in the width of the confidence intervals.

The evaluation of the statistical significance of a trend is not a methodologically straightforward endeavour. Of particular concern is the question of whether or not the test for trend among subjects in different “dose” categories should include or exclude the unexposed category. My view is that it depends on whether or not the study results for Ever/Never exposure are part of the buffet of results presented by the authors. Namely, if the only result presented is a dose-response analysis, then it is appropriate to include the unexposed category as part of the study results. If the Ever/Never result is presented and then a dose-response analysis is conducted, it is preferable to maintain statistical independence of the two analyses by excluding the baseline unexposed category from the dose-response analyses. I will interpret the data from these studies in light of this interpretation of trend tests.

The three smallest studies in Table 6 show no evidence of a dose-response pattern. However, the estimates are so imprecise, as evidenced by the very wide confidence intervals, that they are virtually uninformative regarding the presence or the absence of dose-response.

When looking at the Terry 2013 results, which assemble data from eight teams and 10 studies, the confidence limits are much tighter and the estimates of RR much more precise. The p-value for trend (excluding the unexposed group) is 0.17. Nevertheless, with a reference value of RR=1.0 among unexposed, and with point estimates of RR in four quartiles of cumulative exposure of 1.14, 1.23, 1.22, and 1.32, these results are certainly

compatible with the presence of an underlying dose-response relationship. Note that the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response. Similarly, the Schildkraut 2016 study results, while based on only two lifetime cumulative “dose” categories with point estimates of 1.16 and 1.67, are also compatible with a dose-response pattern.

Trends by duration of exposure: **Table 7** shows the results of those studies that presented RRs by duration of use. The Terry 2013 pooled analysis did not report results by duration of use; however, some of its constituent studies did so and are included here. The numbers in each of the duration categories in each of these studies is quite small, and consequently the RR estimates are very imprecise, with wide confidence intervals. The categorisation of duration differed quite a bit among the studies and it is not easy to compare results between studies. There is no indication of a dose-response relationship in these results. Though, the wide confidence intervals make it impossible to affirm that there is evidence against dose-response. Further, the largest study showing results by duration of use, Wu 2015, did find a significant increase in risk with increasing duration.

Trends by intensity of exposure: **Table 8** shows results of those studies that reported by intensity (i.e. frequency) of usage. This ignores duration of usage. Like the results in Table 7, the results in individual studies are based on rather small numbers and they entail imprecise estimates of RR. Also like Table 7, the pattern of results is equivocal. There is no clear evidence for or against an underlying dose-response.

The Berge 2018 paper also looked at dose-response. They only looked at trends by duration of usage and frequency of usage, analogous to my Tables 7 and 8. However they actually fitted continuous variable models and found that there were significant trends in risk by duration and by frequency of exposure. They did not examine trends by cumulative exposure, and in particular they did not use the results from the Terry 2013 pooled analysis, which in my view is the most informative evidence available on dose-response.

Penninkilampi 2018 looked at risk according to long duration of usage and found no trend. They also looked at cumulative exposure with total number of applications, and they reported a slightly higher RR for women with greater than 3600 applications (RR=1.42)

compared with women who had fewer than 3600 applications (RR=1.32). I cannot determine from the paper which studies were included in this analysis and in particular whether the pooled Terry 2013 dataset was included. While the Terry 2013 and Penninkilampi 2018 papers both contained some results on dose-response, they are not included in Tables 6-8 because they are not original data collection studies; like mine, their's is a review of other studies which are contained in Tables 6-8. As indicated above, all other things being equal, the best metric of the three quantitative ones is the cumulative exposure metric, and that is the one that happens to provide the most statistically reliable data. Thus, the evidence from Table 6 overrides the weaker evidence from Tables 7 and 8. The evidence from the Terry 2013 paper is the most important piece of evidence we have on dose-response. The evidence from the Terry 2013 paper is compatible with the presence of a dose-response relationship between use of powder and ovarian cancer.

6.4 Subtypes of ovarian cancer - in particular, serous invasive tumors

Most studies that provide results on RR between talc powder and ovarian cancer provide results for all types of ovarian cancer combined. Less than half of the published studies have also provided results of the associations between talc powder exposure and various subtypes of ovarian cancer.

To the extent that talc exposure might have different effects on different subtypes of ovarian cancer, there would be a clear advantage to segregating the evidence by type of ovarian cancer and evaluating the evidence for each subtype. The serous-invasive subgroup comprises over half of all cases, and the rest are split among several other histology-behaviour subgroups (mucinous, endometrioid, clear cell, others, and these can be further subdivided by invasive or borderline). Those latter subgroups entail very small numbers each and barely provide enough data, in most studies, to produce informative risk estimates. In those studies, where results were presented by histologic-behaviour subgroups, it is my judgement that there is no strong consistent pattern indicating that one subtype has higher risk than another. Of course, there is variability in point estimates of RR, but on the one hand the variability in RR estimates between ovarian cancer subtypes within studies is not greater than would be expected from chance variability (mostly, the

confidence limits overlap considerably), and on the other hand, from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks.

In the largest assembly of cases subdivided by histologic subtype, the Terry 2013 pooled analysis, the results by subtype were as follows:

- Serous: n=1197; RR=1.24(1.13-1.35)
- mucinous: n=94; RR=1.06 (0.82-1.36)
- endometrioid: n=304; RR=1.20 (1.03-1.40)
- clear cell: n=187; RR=1.26 (1.04-1.52).

Other than serous invasive tumors, there is no other subtype for which there are sufficient numbers of studies and sufficiently precise estimates of RR in each study to provide reliable estimates of the overall RR. While the results for endometrioid and clear cell tumors show risks that are closely aligned with those for serous tumors, the result for mucinous tumors are so imprecise, because of the very small numbers of such tumors, that the estimated RR of 1.06 is very unreliable.

Consequently, and because there were multiple studies apart from Terry 2013 that presented results for serous tumors, I decided to conduct a meta-analysis for serous/invasive ovarian cancers, but not for other subgroups. The meta-analysis on serous invasive tumors will indirectly inform us also about the relative risks for other types of ovarian cancer. Namely, if the RR for serous invasive tumors is similar to that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) will not be very different from the overall RR. If the RR for serous invasive tumors is much greater than that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) are lower than the overall RR. Similarly, if the RR for serous invasive tumors is much lower than that for all ovarian tumors, it will

imply that the risks for other types (the complement of serous invasive tumors) are higher than that for all ovarian cancer.

Table 9 shows all the studies that reported results concerning the link between talc exposure and serous/invasive tumors. There were 8 informative studies, including Terry 2013, which carried by far the most statistical weight. The meta-RR estimate for serous/invasive tumours was 1.25 (1.1.15- 1.36). This is very similar to meta-RR for all ovarian tumors, albeit based on a smaller number of informative studies. Thus there is no persuasive evidence in these studies, taken as a whole that the effect of talc differs by histologic subtype of epithelial ovarian cancer. That is, with such a tiny difference in RRs between that for all ovarian cancers combined and that for serous invasive ovarian cancers, it can be safely inferred that the RR for other types of ovarian cancer (the complement of serous invasive) would not be far from the overall RR of 1.28.

6.5 Conclusion from meta-analyses and dose-response considerations

My opinion, based on up-to-date data and meta-analyses, is that the RR between ever perineal use of talcum powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). This result is highly statistically significant.

We can rule out random variability as a possible explanation for the apparent excess risks. Further, the examination of results according to the “amount” of exposure, and notably the cumulative exposure variable used by Terry 2013, shows that the higher the exposure, the higher the risk.

Such a pattern of findings can have only two possible explanations: it must be the result of some sort of bias or confounder that operated in multiple studies or it must be the result of a real causal association.

7. Misconceptions and possible biases

In reaching my opinions, I have objectively looked at the data and scientific literature and considered the points of view of others who do not share the conclusions I have reached. There are generally two sources of disagreement: misconceptions of epidemiologic or

statistical concepts which I address below in Section 7.1 and professional judgement of the likelihood of errors and biases in the various epidemiological studies, which I address in Section 7.2.

7.1 Some prominent misconceptions in reviewing the evidence

Table 10 lists some prominent misconceptions, and I will address them here.

Misconception: "Cohort studies are more valid and informative than case-control studies."

As can be seen in Table 2, the case-control studies tended to produce higher RR estimates than the cohort studies. It has sometimes been claimed that cohort studies are more valid than case-control studies. There is no theoretical or practical reason why such a blanket assertion should be universally true. There are many factors that influence the validity of a particular result in a particular study and it cannot be reduced to any simplistic assertion that cohort studies are more valid than case-control studies, or vice versa. In the next section, I will go through a number of potential sources of distortion of results from epidemiologic studies, and I showed that some of them might occur in cohort studies, some in case-control studies, and some in both. Some of these distortions very likely occurred in some or all of these studies that provide data on talc and ovarian cancer. On balance, I believe the results of each of these case-control studies concerning female use of powders and ovarian cancer are credible, and perhaps more so (for reasons given in section 7.2), than the analogous results of each of these cohort studies.

Misconception: "Hospital-based case-control studies are more valid and informative than population-based case-control studies."

In a case-control study, the design objective is to define a study base, or a population base, in which the cases might occur, and to identify representative samples of cases and of controls in that study base. The purpose of a control group is to provide an estimate of the prevalence of exposure to the factor under study in the base population that gave rise to the cases. In many instances, the best source of controls for case-control studies is a population list of some sort. But sometimes using a population list is not feasible or

desirable, and an alternative can be to select controls from among hospital patients with conditions other than ovarian cancer. This was done in some of the ovarian cancer case-control studies.

The most common generalization made by epidemiologists is that population-based case-control studies are more valid than hospital-based case-control studies. In fact, neither this nor the opposite statement that I articulated as a Misconception, is universally correct. Validity of a case-control study depends on the specific design features and circumstances of the study.

It is possible that some types of hospital controls have patterns of usage of powders that are different from those of women in the general population, either because the powders are actually causally associated with the diseases that those women have or because their disease or condition that led them to be hospitalised induces some women to take up the use of such powders. If such a mechanism was present in a hospital-based case-control study, it would likely lead to an artificially attenuated RR, not an artificially inflated RR.

Misconception: "Counting the number of statistically significant results is a valid way of assessing consistency of results among multiple studies."

This misconception betrays a lack of understanding of statistical significance. As can be seen in Table 2, several of the individual studies listed in my meta-analysis did not find a statistically significant increase in RR. This has been cited by some as evidence that there is no real causal link.

In fact, meta-analysis is a method that was developed precisely because counting significant results is an invalid way of synthesising knowledge. Namely, a result from a single study may fail to achieve statistical significance either because there is no risk in that study, or because the statistical power of the study was limited. Meta-analysis was developed in order to combine evidence from multiple studies that may be under-powered on their own, but when combined show an effect that might be statistically significant. The meta-analysis cannot conjure a statistically significant meta-RR if the individual study RRs do not systematically lean in the direction of an excess risk, and they do so in the area of talc and ovarian cancer to a degree that cannot be explained by random fluctuation.

Misconception: "You cannot prove causality with an RR less than 2.0."

There is nothing in epidemiologic theory or practice that justifies such a statement. Indeed, this assertion about an $RR \geq 2.0$ threshold does not exist in epidemiology. There are many well-established causal relations where the RR is less than 2.0. Table 11 lists a number of such examples. In clinical medicine also, it is very common to strive to find therapies that reduce the risk of death from some disease by as little as 10%, and several such discoveries are well documented and have been integrated in medical practice, even though the change in risk is small.

Misconception: "If a product has been used for a long time it must be safe."

It has been argued that since talc powder has been used for many decades by millions of women (and men and children), it has stood the test of time and should be considered safe. This is a specious argument.

Most agents in our environment or in our lifestyle which are now considered dangerous were used for decades or centuries without falling under a cloud of suspicion. These include such factors as cigarette smoking (many cancers and cardiovascular disease), asbestos (lung cancer), sunlight (skin cancer), ingesting very hot liquids (esophageal cancer), and many others.

Misconception: "Government agencies provide the most reliable and authoritative statements regarding the lack of carcinogenicity of talc."

Various national and international agencies have websites which list carcinogens. Examples are: National Cancer Institute (NCI), National Toxicology Program Report on Carcinogens (NTP-RoC), International Agency for Research on Cancer (IARC). It can be argued that these agencies, which undoubtedly have scientific credibility, would not put on their websites information that is out of date or invalid. However, that claim is false.

IARC has a rigorous evaluation process which is considered quite authoritative throughout the world, including in the U.S. But the evaluation is carried out at a certain point in time. The last time talc was evaluated by IARC was in 2006. Based on the evidence available then, the panel rated talc as a "possible" carcinogen. Additional evidence has been accumulated

and come to light since then, but there has not been a new evaluation by IARC. (There are potentially thousands of agents to evaluate, and IARC has resources to only evaluate a few each year. Thus they cannot keep re-evaluating the same ones as soon as new evidence is published.)

NTP-RoC is a congressionally-mandated program whereby the agency is obligated to periodically publish lists of known and suspected carcinogens. Unlike IARC, it appears that the people who make the decisions are internal RoC scientists, rather than external experts, with advice from outside experts. Also unlike IARC, the biennial reports only contain listings of those agents that have been deemed to be definite or likely carcinogens, so there does not seem to be a statutory listing of all agents that have been considered. From the minutes of a meeting of the Board of Scientific Counsellors of NTP held in 2000, it appears that the issue was deferred. I am not aware that the RoC has conducted a subsequent review of talc; although, when renominated in 2004, NTP deferred to IARC.

NCI provides a website for doctors where they indicate for each type of cancer, what are the known risk factors. Based upon my understanding, they do not carry out a rigorous evaluation along the lines of the IARC evaluations or even the NTP evaluations. It is a rather superficial process compared with the IARC process and it depends on the existing knowledge of the committee members which in a short time opines about possible associations between each of the scores of cancer types and scores of potential risk factors. This is not to argue that the members of these committees are less expert than the members of the IARC committees, but the NCI committee members have a short time (apart from their main jobs) to review hundreds of possible factor-cancer associations, whereas the IARC committee members have weeks to review just a few.

Scientists and public health agencies regularly consult the IARC evaluations and those of the NTP. The NCI website for doctors is not considered an up-to-date and cutting edge source of information. This is, of course, no reflection on the gravitas of the NCI as a whole, which has much more invested in its original research mission than in its website for doctors.

There are other organizations which may put some information about causes of cancer on their websites. Importantly, I have not seen any agency or organization, including the FDA, that conducted a rigorous evaluation of the epidemiologic and non-epidemiologic studies like we did at IARC in 2006.

Misconception: "A biological mechanism must be proven before we can establish causality"

There are innumerable examples in medical history of discoveries of risk factors or treatments that did not require knowledge of the mechanisms of pathogenesis in order to determine causality. I have compiled a few such examples from medical history and show them in **Appendix C**.

Very often, the initial suggestion was met with scepticism from the vantage point of biologic plausibility. In fact, very seldom have the essential features of biologic plausibility been worked out by the time the epidemiology has convincingly demonstrated that the association is causal. This can be asserted for the early discoveries such as the cancer causing effects of certain chemicals in dye production facilities, certain metals in various heavy industry facilities, certain emissions of combustion of fossil fuels, ionising radiation, and even cigarette smoking. In most of these examples, it was decades after the epidemiologic evidence became convincing that credible mechanistic theories were proven; though, for some, the biologic mechanisms remain unknown.

Indeed in the guidelines of the IARC Monographs, it is stated that if there is "sufficient" evidence of a risk of cancer from epidemiologic studies, then irrespective of the evidence from animal experimentation and other biologic evidence, the agent in question should be considered a Group 1 carcinogenic agent. My point here is that the demonstration of a proven biologic mechanism is not a prerequisite for demonstrating that an agent is a human carcinogen. Reliable empirical epidemiologic evidence of an association is a sufficient basis for demonstrating causality; the presence of a credible biologic mechanism enhances the degree of proof, though that often lags decades behind the general recognition of causality, as exemplified by the examples in Appendix C.

It is not my opinion that we should ignore or set aside consideration of biologic plausibility. As Hill (1965) indicated in outlining the thought process for establishing causality, biologic plausibility is one of the dimensions to be considered. But, he also cautioned that, “this is a feature I am convinced we cannot demand”. Thus, as I have done in other contexts in regard to other putative carcinogens, I am able to draw causal inferences about talc irrespective of whether a causal mechanism has been proven.

Misconception: “Bradford Hill criteria comprise a checklist of necessary conditions”

As I explained in section 4.2, the “aspects” that Hill listed are not “criteria” and they are not necessary. This point has been made and is widely accepted by epidemiologists. The list of “aspects” in Hill’s original paper have been rephrased and reworked in many textbooks and by most agencies that refer to them. They provide a framework and not a checklist.

7.2 Alternative explanations - Biases and errors

Before inferring that the strong statistical evidence that use of powder in the perineal area by women is associated with ovarian cancer may represent a causal relationship, I considered alternative explanations for these observations. In this section I will consider a number of potential sources of distortion of the risk estimates, under various rubrics. Some of the potential sources of distortion are unique to cohort studies, some are unique to case-control studies, and some can affect both types.

7.2.1 Bias due to non-response or non-participation

This is a potential source of bias in case-control studies.

Among all potential cases and controls who meet the study’s eligibility criteria, some participate and some don’t. The most common reasons for non-participation are: refusal; inability of the researchers to contact the person because they moved or are too sick or died or are otherwise unavailable; if access to the subject is via the treating physician or medical staff, there could be obstacles at that level. If the factor under study, hygiene powder use, is correlated with the likelihood of participation and if the participation rate is low, this could lead to biased estimates of RR. Such bias could artificially inflate or deflate the RR depending on how the various variables are related to each other. If response rates

are low, say below 70%, and differential both by case-control status and by exposed – non-exposed status, this could lead to biased RR estimates. For such a bias to explain the outcomes seen, it would require quite strong associations between likelihood of participation and powder use, and quite strong differences in such associations between cases and controls. In my opinion, it is very unlikely in the context of these studies that response rate differentials would be great enough to induce such large bias.

7.2.2 Recall or reporting bias

This is a potential source of bias in case-control studies.

Because the exposure history is collected retrospectively, it is subject to both non-differential recall errors (see below), and to recall or reporting bias between cases and controls. Cases and controls may have different motivation and proclivities to recall and report use of powders. If it were true that cases had a greater tendency to over-report powdering history or if controls had a greater tendency to under-report powdering, then this would lead to an artefactual exaggeration of the RR.

There are a few possible causes of such differential reporting. First, it might be hypothesized that there is a general tendency for cases in case-control studies to acknowledge behaviours or exposures with much greater frequency than controls just because they are more invested in the research than are controls. They may wrack their brains during the interview to find instances of the queried behaviour or exposure that controls don't pay much attention to during the interview, because the controls just "want to get the interview over with". If this were the case, we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies. But in my experience, this does not occur. (I have conducted many case-control studies, each study eliciting information on many lifestyle factors and exposures. It has not been the case that cases systematically report more exposures than controls.) Furthermore, and more pointedly, if such a phenomenon were operative in these case-control studies of ovarian cancer, we would see elevated RRs when women were questioned about the use of powders on other parts of their bodies than the perineal area. In fact, several studies did ask such questions. In the Terry 2013 analyses, based on very large numbers of women, the

overall RR for ever use of hygiene powder on non-genital areas of the body was 0.98 (0.89-1.07), in stark contrast to the analogous result for genital use of 1.24 (1.16-1.33). In other words, when questioned about powdering in non-genital areas, controls were as likely to say “yes” as cases. Clearly there was no tendency for cases to indiscriminately report exposures more frequently than controls.

A second possible reason for such a situation to arise is if there was widespread knowledge about powdering being under suspicion for ovarian cancer. In such a situation women who have heard about this might internalize the notion that powdering may have caused their cancer, and they might ruminate with such intensity on the notion that they might imagine that they had used powders at some point in the past. But for most of the period of data collection in these studies, there was very little public discussion of a possible linkage between powdering and ovarian cancer and I doubt if more than a handful of the thousands of women interviewed in these studies would have heard of such a hypothesis before being interviewed.

In my opinion recall bias is not likely to have produced the kinds of RRs we see in these studies.

7.2.3 Non-differential (or random) error in recall or reporting of exposure to powders

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

Reporting past history of activities and exposures is always subject to some degree of error; it can result from ambiguity or misunderstanding of the questions, failures of memory, or inattention. And this is certainly true for history of powdering. If such error is non-differential (i.e. equally present for cases and controls in the case-control context) it has an effect on RR estimates that is rather predictable. Namely, as I explained above, it has the effect of artifactually decreasing the RR. The degree of attenuation is roughly proportional to the degree of error or misclassification. If there really is a causal association between powdering and ovarian cancer, then we can be rather certain that the true RR is higher than what we can see in the various studies that have reported RRs.

Furthermore, we might make some reasonable inferences about the impact of reporting error on dose-response trends as well as on the overall RR. It is reasonable to surmise that the amount of reporting error is quite a bit higher for the details of past usage (duration of usage, intensity and frequency of past usage) than it is for the simple fact of usage. That is, there is less error in a woman's report of whether or not she ever used powders on a regular basis than in her report of the details of the usage, even if powdering behaviour may be a relatively stable habit. The consequence of this is that the RR based on ever/never usage (Table 2) is less subject to artefactual attenuation than the RRs based on categorizing the duration or intensity or cumulative amount of usage (Tables 6-8). This is a possible explanation of why there has been a much clearer signal of elevated RR for ever/never usage than there has been for dose-response.

There is likely to be more measurement error of exposure to powders in cohort studies than in case-control studies, for several reasons. First, because the cohort study questionnaires attempted to broach topics that could be relevant to many types of cancer and indeed many diseases, the questions posed in the cohort study questionnaires about talc powder use tended to be much briefer and probably less effective at eliciting valid information than the questionnaires used in case-control studies of ovarian cancer. For instance, the cohort studies did not elicit information on timing or duration of past usage, and one of the cohort studies did not even attempt to elicit information about use of talcum powder products over 12 months before the interview. Second, whereas a case-control design involves a woman looking backwards over her life from the time of incident cancer onset and thereby addressing the entire relevant period of potential exposure, the woman in a cohort study reports on her past usage as of a certain point in her life, but there may be 10-20 years subsequent in which her habits could have changed, and of which the cohort study has no knowledge. The women in the cohort studies were "locked into" their exposure category at baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users. Accordingly, the longer such subjects are followed, the more likely such misclassification is to occur.

The age at which information is collected is a relevant consideration. In most case-control studies, the mean age of the study subjects was between 50 and 60. In the NHS cohort study the mean age at baseline questionnaire was around 40 and in the WHI it was over 60. In each study, women were asked about their past history of powder usage. Clearly the WHI women had a further stretch of time to consider than the women of the NHS and even of the case-control studies.

A particular form of measurement error may well have occurred in the Gonzalez 2016 study and produced even more attenuation of RR estimates. Namely, in their brief questionnaire on talc exposure, the question was formulated to ask women about their use of powders in the 12 months preceding the interview. While exposure to talc over the past 12 months may be correlated with exposure over the entire etiologically relevant period, which might go back decades in the life of the woman, the correlation is probably weak, and this is another source of measurement error.

7.2.4 Short follow-up periods for disease ascertainment

This is a potential source of bias that would affect cohort studies.

In a cohort study, if the period of follow-up after baseline is relatively short; and if the latency period between exposure and cancer is long, the excess risk may not be detectable because cases that would occur after long latency have not had time to occur. If this did occur, it would lead to an artificially low RR estimate.

This could have been an issue in the initial publication from the NHS, the Gertig 2000 paper. As of the Gates 2008 and Gates 2010 analyses of the NHS, the follow-up period was probably long enough and this bias should have abated. For the WHI study it was likely an issue in the Houghton 2014 paper, and it would remain so until there is much longer follow-up. It would also be an issue in the Gonzalez 2016 paper from the Sister Study, which had only 6 years of follow-up after exposure was ascertained.

7.2.5 Diagnostic error

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

The diagnosis of cancer is never error-free. And details of histology and staging are even more error-prone. Further, there are trends in diagnostic criteria and methods over time, as well as in the terminology and classifications used. So what we observe in these various studies of ovarian cancer represents imperfect estimates of true biologic/pathologic status. The impact of such “errors” is mainly the same as exposure measurement error, namely it would tend to artificially reduce RR estimates. Since most case-control studies start from hospital-based cancer diagnoses as the point of entry, they usually have reasonably valid diagnostic information.

In general, cohort studies tend to be more vulnerable to this source of error and bias, because disease diagnosis information is often obtained from sub-optimal sources, such as the information provided by the study subject or her family, or information obtained from death certificates. In the three cohort studies included in the meta-analysis, there were high quality verifications of diagnostic information that had been provided by the women or their families. But such verification may not be as reliable as information coming straight from hospital pathology or oncology services. I expect that this was not a major issue here, but to the extent that it did operate, it too would have led to some additional attenuation of RR estimates, as I explained above.

7.2.6 Initiation of powdering as a result of ovarian cancer

This is a potential source of bias that would affect case-control studies.

It has been speculated that women with early symptoms of ovarian cancer might take up the use of powders to help with relief of their symptoms. If so they might report that they used powders before their cancer was diagnosed and this could artificially inflate the RRs. While the women are usually questioned about the period before their cancer was diagnosed, there could be some “telescoping” so that women who start dusting after diagnosis respond in the affirmative to the questionnaire.

In the same vein, it has been speculated that treatment for ovarian cancer might produce side effects that could be relieved by powdering. And again, it might be posited that women ignore the instruction to refer the exposure question to the time before the onset of the cancer.

If the early symptoms of ovarian cancer provoke some women to start dusting the perineum to relieve some of the discomfort, or if the treatment provokes women to start dusting, this would lead to an artefactual excess RR.

I have not found any empirical evidence to support this hypothesis.

In the few datasets I have seen which describe the age distribution of initiation of powdering, there were very few patients who started in the year or two before diagnosis of the cancer. I am inclined to believe that it is virtually a non-issue, and that if it operated at all, it would only have operated on a handful of the thousands of women who were part of the various case-control studies.

7.2.7 Confounding

This is a potential source of bias that would affect both case-control and cohort studies.

If women who use powders are also more likely to be exposed to other risk factors for ovarian cancer, then it might distort the relationship between powdering and OC. The direction and the degree of distortion (bias) that would be induced depends on two components, a) the true association between the confounder and ovarian cancer, and b) the association between the confounder and dusting behaviour. Thus, depending on the direction of these two component associations, the confounding can result in artificially decreased or increased RRs. Typically, the degree of confounding is much lower than the strength of the association between the confounder and ovarian cancer. In order for a confounder to induce an artificial RR of 1.25 for dusting, it would have to have an RR much greater than 1.25 with ovarian cancer and a fairly strong correlation with dusting behaviour. Given that the main studies have controlled for the main risk factors, I consider it unlikely that this operates. Table 1 shows the covariates that were controlled for in each study, and while there is some variability between studies in the list of covariates, the main known potential confounders (age, BMI or weight, parity) have been controlled for in almost all studies. It should be noted that while smoking is a well-established risk factor for many types of cancer, it is not a risk factor for ovarian cancer; thus, there is no need to control for smoking status in studies of ovarian cancer.

A thorough and reliable investigation of potential confounders was conducted by Cramer (2016); in the large database of New England-based studies, they explored the potential confounding effect of a host of personal characteristics including demographic, reproductive, hormonal, comorbidities, activities, and exposures. None of the covariates that they explored had any meaningful confounding effect on the association between talc and ovarian cancer.

7.2.8 Publication bias

This is a potential source of bias that would affect case-control and cohort studies.

This refers to the tendency for some evidence never to “see the light of day”. Namely, when results are “negative” or “null”, it may be that investigators never bother to submit them for publication, or alternatively, that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small. In the talc-ovarian cancer literature this would have been more likely in the pre-2000 era when there was much less scientific interest in the hypothesis linking talc to ovarian cancer. As a sensitivity analysis, I conducted a meta-analysis on the subset of studies in Table 2 that had at least 20 exposed cases. That is, I eliminated the studies from that stratum of the universe of studies that were most susceptible to publication bias. The resulting meta-RR was almost identical to those shown in Table 4. Because this has been a somewhat controversial topic in epidemiologic circles over the past 20 years, I doubt if there were large important studies with null findings on talc-ovarian cancer that went unpublished.

In their meta-analyses, Berge 2018 and Pennikilampi 2018 both showed funnel plots of the results. These are meant to detect so-called publication bias. Both of those analyses concluded that there was no publication bias.

In summary, I consider that the observed association between talc and ovarian cancer is not an artefact due to publication bias.

7.2.9 Summary comments regarding biases and errors

While the results of epidemiologic studies strongly supports the hypothesis of an association between perineal use of powders and risk of ovarian cancer, we must be wary of potential sources of error and bias that can distort an association before concluding that this association is causal. I have therefore gone through the plausible sources and types of error and bias that could potentially explain the positive association seen across the relevant studies to ascertain how likely it is that each such type was actually operative and, if so, what the nature of the impact may have been. These evaluations are based on my professional opinion as an epidemiologist having conducted, reviewed, and evaluated many hundreds if not thousands of epidemiologic studies.

Of the various types of error listed, some could artificially inflate the RR estimates and some could artificially decrease the RR estimates. Some are likely to have occurred and some are unlikely to have occurred. The one that certainly occurred and that has a non-trivial attenuating effect on RRs is random exposure misclassification (section 7.2.3). As explained above, if there is a true association, then the true RR is almost certainly greater than the estimates seen in these studies and in the resulting meta-analyses. Other types of error and bias that are highly likely to have occurred are the two that are specific to cohort studies. Namely, the Nurses' Health Study papers (Gates 2008 and Gates 2010) almost certainly suffered from an attenuated RR estimate because of the compromised reference category of "unexposed" while the Women's Health Initiative paper (Houghton 2014) and the Sister Study paper (Gonzalez 2016) almost certainly suffered from a too short follow-up period (section 7.2.4). In my opinion, the occurrence and the possible impact of other listed types of bias and error are more speculative, and less likely.

Consequently, in my opinion, the observed association between talcum powder products and ovarian cancer is unlikely to be explained by any methodological problems with the studies.

8. Bradford Hill guidelines applied to talc and ovarian cancer

The Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) states: "There is no formula or algorithm that can be used to assess whether a causal inference is

appropriate based on these guidelines.” These guidelines are simply aspects that might be considered in assessing causality. I will give my assessment of how the evidence regarding talcum powder products and ovarian cancer fit into those aspects. I will use the version listed in the Reference Manual on Scientific Evidence. While there is no objective basis or scientific precedent or “scientific jurisprudence” for quantification or weighting of the various “aspects”, to help the reader to understand the relevance that I attached to each “aspect” in my evaluation, I will provide an informal ranking of the importance that I attach to each aspect, in the specific context of the assessment of causality of evidence regarding talcum powder products and ovarian cancer. I will list the aspects in descending order of importance that I attach to them.

My opinions are briefly summarized in **Table 12**.

Highly important aspects in my weighting

There is a set of B-H aspects that are utterly inter-related and cannot be disassociated one from the other. In combination, they represent the most important aspect to consider in evaluation of causality of talcum powder for ovarian cancer. These include strength of association, dose-response, consideration of biases, and consistency of findings.

Strength of the association. This can embody both the magnitude of the RR and its statistical significance. The meta-RR estimate is 1.28. That means that the best estimate from the epidemiologic literature is that women who regularly used talcum powder products in the genital area had 28% higher risk of ovarian cancer than women who did not use such powders. As I illustrate in Table 11 with a few examples, this RR is in line with many well-recognized risk factors for cancer and other diseases. For example, it is well accepted now that people living in an urban neighborhood in which the air is highly polluted with particulate matter have between 5% and 10% excess risk of lung cancer compared with people living in a less polluted urban neighborhood. Also, it is well accepted now that workers exposed to a solvent called trichloroethylene have about a 40% higher risk of kidney cancer compared with workers not exposed to trichloroethylene. Thus, the 28% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. This increased risk as manifested by the meta-RR is highly

statistically significant. (Note that the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.) Such a high and significant meta-RR could not have occurred by chance. This is a very important factor in how I view the evidence of causality, and it supports causality.

Dose-response relationship. If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency). The most sensitive of these metrics is the cumulative amount. I evaluated the published studies reported on risks according to the different metrics. By far, the most important set of results on dose-response is that from the Terry 2013 pooled analysis of 10 studies using the cumulative exposure metric. And, the next most important from a statistical weight point of view is that from Schildkraut 2016. In both of those studies, there is a clear indication of increasing risk with increasing cumulative exposure. Since the statistical power to detect a trend is less than the power to detect an overall risk, it is not surprising that the p-value for trend does not attain the conventional 0.05 level, but it remains true that these studies support a dose-response. This is an important consideration in my assessment of causality, and the evidence on dose-response that our IARC committee had available in 2006 was much less persuasive than the evidence available now.

Consideration of alternative explanations - absence of bias. There are many potential sources of bias in observational research, including in epidemiology. It is important to consider the presence of bias in each study performed or reviewed in an evaluation of causality. The possibility of bias is so multifaceted that it is impossible to reliably assign an explicit score to the likelihood of bias in a study or in a body of studies. It is also important to understand that identifying a potential source of bias is not tantamount to identifying the presence of bias. In section 7.2, I have reviewed the potential role of several types of biases and errors

that can bedevil such research. I concluded there that none of those factors would cause the apparent associations.

Consistency of findings between studies (or replication of findings). Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship. In my review of the published epidemiological studies and meta-analysis, I am impressed by the consistently elevated risk across studies. Almost all of the 30 or so studies have produced an RR greater than the null (neutral) value of 1.0. If there really were no association between talcum powder use and ovarian cancer, we would expect to see as many RRs lower than 1.0 as higher than 1.0. The pattern we see is like flipping a coin 30 times and getting a heads 28 or 29 times. The individual study RRs are not all necessarily statistically significant, but that is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4. It is the statistical significance of the meta-RR, representing the combined evidence that has the requisite power, and that excess RR is highly statistically significant. I place great weight upon this evidence of causality and, here, believe it to be amongst the most important findings.

Moderately important aspects in my weighting

Temporal relationship. Exposure should be seen to have preceded disease. It is almost a logical truism. This is the only aspect that Bradford Hill considered to be necessary. In all of the studies I reviewed, the information elicited about talc exposure concerned the time period before cancer onset. Since it is so obviously important, the reader may wonder why I place lesser weight on this aspect. It is simply because the presence of this condition of temporality is so obvious in these studies.

Biological plausibility (coherence with existing knowledge). It is both conventional and natural to consider whether any putative association is biologically plausible. The notion of

biological plausibility is multi-faceted. In the case of talcum powder products and ovarian cancer, it can include such issues as: how such powders have been used, female anatomy and physiology, toxico-kinetics and toxicology of talc, in vitro and in vivo mechanisms of carcinogenesis, and others.

The first thing to note about this aspect that Bradford Hill listed is that it is called “biological plausibility”, not “biological proof”. That is, there was never any implication that a determination of causality should rest on a demonstrated proven biological mechanism. Hill was always reserved about this aspect, stating that it was not an essential prerequisite to establishing causality. As I have mentioned above, it has been common in the history of medicine and epidemiology for the elaboration of a validated biological mechanism to come much later than the discovery and demonstration of a causal association. Appendix C gives a handful of such examples but there are scores more.

Insofar as the issue of talcum powder products and ovarian cancer is concerned, there is evidence to support a few biologically plausible mechanisms. First of all, there are two possible routes that talcum powder products can take to reach the ovaries. There is published evidence that talcum powder products (and its constituents and contaminants) that are applied to the vaginal area can migrate from there to the fallopian tubes and ovaries (Venter 1979; Henderson 1986; Heller 1996) or to pelvic lymph nodes. (Cramer 2007) In addition, as has been hypothesized and partially demonstrated in the discussion of asbestos and ovarian cancer, such particles might reach the ovaries via inhalation and translocation. (Miserocchi 2008; IARC 2012) Once the particles reach the ovaries, carcinogenesis can be triggered by the inflammation engendered by the particles. (Ness 1999; Ness 2000) There is considerable evidence that inflammation is an important mechanism for carcinogenesis (Coussens and Werb 2002; Grivennikov 2010). Alternative plausible mechanisms of carcinogenicity include talc induced oxidative stress (Buz’Zard 2007; Saed 2017; Fletcher 2018), and genotoxicity (Shukla 2009).

The evidence that commercial cosmetic talcum powder products have been shown to contain asbestos, fibrous talc, and heavy metals (Blount 1991; Paoletti 1984; Longo et al 2017, Crowley report 2018) provides a reasonable basis for hypothesizing that these

chemicals may contribute to the carcinogenicity of the talcum powder products. Asbestos is a well-known carcinogen, as are chromium and nickel compounds. It is plausible that any of these, in contact with the ovaries, can be carcinogenic.

The fact that there are credible biologically plausible mechanisms by which talcum powder products can reach the upper genital tract causing an inflammatory response, along with the presence of asbestos fibres and other carcinogens is an important consideration in support of my opinion that the genital use of talcum powder products can cause ovarian cancer.

Aspects of lesser importance in my weighting

Cessation of exposure. It is rare that there is valid evidence available to assess the impact of cessation of exposure in an observational study. In the studies on talcum powder and ovarian cancer, there is no evidence one way or the other concerning the effect of cessation of exposure. This aspect is not applicable and I place almost no weight on it.

Specificity of the association. This aspect is premised on the notion that an agent-disease association is more likely to reflect a causal association if the agent is not also associated with other diseases. In the 1960's, this seemed like a reasonable argument. In light of evidence from the past 60 years, this argument is no longer made and this aspect has fallen out of usage with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

So, I do not place much stock in this aspect. However, if I did, I would have to say that genital exposure to talc is associated with ovarian cancer and no other morbidity, which supports the 'specificity' of the relationship."

Analogy

Hill argued that if the agent is similar to another agent that has been shown to be a cause of the disease, then the agent under investigation is more likely to be a cause. The fact that exposure to asbestos fibers can cause cancers in lung, larynx mesothelial tissue and ovaries (IARC 2012) can indicate that, by analogy, talc, which is similar in some respects, might be

able to induce carcinogenesis. Thus, there is an argument for an analogy between talc and asbestos. While this aspect supports causality in Hill's framework, I consider it much less important an aspect than the ones listed above.

Coherence with other types of knowledge: Coherence with other knowledge can encompass a multitude of possibilities. This aspect is both vague and very open-ended, with no real operational instruction on how to use it. Hill gave an example in his paper, but the example was only applicable to tobacco and lung cancer. This is an aspect that, if it can be demonstrated, can enhance the likelihood of causality, but its absence cannot detract from causality. I don't consider it to have much weight in this context.

9. Contrast with IARC Monograph and other reviews

The 2006 IARC Monograph meeting, which I chaired, found that a causal relationship was "possible" between perineal talc powder exposure and ovarian cancer. I concurred with that evaluation.

It is now my professional opinion, based on the totality of the evidence that, to a reasonable degree of scientific certainty, the causal relationship between perineal talc powder exposure and ovarian cancer is "probable. "

What has changed in the years since the IARC review?

The RR estimates in Table 2 are remarkably consistent in showing a highly statistically significant excess risk. The number of published study results and scientific literature addressing the epidemiology, toxicology, molecular biology, and mechanistic studies has increased since 2006, and the evidence of excess risk has been consistently demonstrated across the past three decades.

The various possible biases that are on the table remain substantially similar to the ones that were considered by the IARC panel. At the time, we were not convinced that the apparent excess risk could be explained by those potential biases or confounding. As stated above, my review of the relevant studies and potential biases has led me to conclude that bias does not explain the consistent increased risks seen across the credible studies.

There is important new information with regard to the issue of dose-response. Contrary to the impression that the IARC panel had of a total absence of dose-response, and even a possible trend in the opposite direction, the results of three recent publications, Terry 2013 and Schildkraut 2016, using cumulative exposure metrics, and Wu 2015 using duration of exposure, all demonstrate a clear compatibility with a dose-response relationship. The recent meta-analysis of Berge 2018 supports the presence of dose-response in both duration and frequency of use. The most convincing of these is the Terry 2013 pooled analysis, which assembled a larger dataset than all other attempts to assess dose-response combined. Clearly, earlier reviews could not have integrated the results from these recent studies.

It is my opinion, based upon the above the data, there is evidence of a dose-response relationship. Penninkilampi 2018 has recently expressed a similar opinion.

10. Conclusion

The totality of evidence demonstrates that perineal or genital use of talcum powder products is associated with ovarian cancer. Based on contemporary data, my estimated RR between ever perineal use of talc powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). The body of epidemiologic evidence is remarkably consistent in demonstrating an excess risk. The evidence summarized in Table 6 is compatible with the presence of a dose-response relationship between cumulative exposure to talcum powder products and ovarian cancer. There are various potential sources of bias in these studies, some of which could have inflated the true RR estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to deflate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies. Additionally, there are biologically plausible mechanisms by which talcum powder products can cause ovarian cancer.

Based on the totality of the evidence, it is my opinion, to a reasonable degree of scientific certainty, that the perineal use of talcum powder products can cause ovarian cancer. Given the seriousness of ovarian cancer and its associated morbidity, this causal risk represents an important public health issue.

11. Tables

Table 1. Steps in my evaluation of general causation between talcum powder product use and ovarian cancer

1. Identify all epidemiology study papers that present results on talc and Ovarian Cancer.
2. Extract all RR results from every paper into a database.
3. Determine which of the papers and results present truly independent relevant results.
4. Extract from each study the RR for Ever/Never use of talc in the genital area in relation to OC risk.
5. Conduct a Meta-analysis.
6. Examine the evidence about a possible dose-response relationship.
7. Consider issues of bias, confounding and other sources of error in the various studies.
8. Consider relevant opinion pieces, review articles, and agency reports.
9. Consider opinions from experts regarding possible biological mechanisms.
10. Consider all relevant aspects of association to infer causation.
11. Write report.

Table 2. Relative risk estimates between ever regular use of talcum powders products¹ in the perineal area and ovarian cancer², from various studies used in the Main Meta-analysis or in one or more of seven sensitivity analyses

Author	Included in Main meta-analysis	All tumours			
		Number exposed cases	RR ³	95% CI ⁴	
Booth 1989	?	141	1.29	0.92	1.80
Chen, 1992	?	7	3.9	0.91	10.6
Cook 1997	?	159	1.5	1.1	2.0
Cramer 1982	?	60	1.55	0.98	2.47
Cramer 2016		642	1.33	1.16	1.52
Gates 2008		57	1.24	0.83	1.83
Gates 2010	?	231 ⁵	1.06	0.89	1.28
Godard 1998	?	18	2.49	0.94	6.58
Gonzalez 2016	?	17	0.73	0.44	1.2
Harlow 1989	?	49	1.1	0.7	2.1
Harlow 1992	?	114	1.5	1.0	2.1
Hartge 1983	?	7	2.5	0.7	10.0

Author	Included in Main meta- analysis	All tumours			
		Number exposed cases	RR ³	95% CI ⁴	
Houghton 2014	?	181	1.12	0.92	1.36
Mills 2004	?	106	1.37	1.02	1.85
Ness 2000	?	161	1.5	1.1	2.0
Purdie 1995	?	467	1.27	1.04	1.54
Rosenblatt 1992	?	22	1.7	0.7	3.9
Schildkraut 2016 A ⁵	?	248	1.44	1.11	1.86
Schildkraut 2016 B ⁵		128	1.19	0.87	1.63
Shushan 1996		21	1.97	1.06	3.66
Terry 2013	?	2600	1.24	1.15	1.33
Terry-AUS 2013		705	1.13	0.92	1.38
Terry-DOV 2013		272	1.13	0.93	1.36
Terry-HAW 2013		74	0.99	0.70	1.41
Terry-HOP 2013		194	1.34	1.07	1.67
Terry-NCO 2013		195	1.37	1.05	1.80
Terry-NEC 2013		755	1.28	1.12	1.47
Terry-SON 2013		197	1.35	1.03	1.76

Author	Included in Main meta- analysis	All tumours			
		Number exposed cases	RR ³	95% CI ⁴	
Terry-USC 2013		208	1.36	1.06	1.74
Tzonou 1993	?	6	1.05	0.28	3.98
Whittemore 1988	?	67	1.36	0.91	2.04
Wong 1999	?	157	1.0	0.8	1.3
Wu 2015	?	701	1.46	1.27	1.69

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. In this table we report the result for all types of ovarian cancer combined. With the exception of the Harlow 1989 study that was restricted to borderline tumours, we have assumed that all studies included both borderline and invasive tumours, although this was not always clear in the publications.
3. RR or OR.
4. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
5. Estimated based on Table 1 of Gates 2010.
6. The Schildkraut 2016 case-control study presented two sets of results that both have some legitimacy for the present purpose. Schildkraut 2016A shows the results for all subjects who were interviewed in the study from 2010-2015. Schildkraut2016B shows the results for those subjects who were interviewed before 2014, and who, according to the authors, were not susceptible to having been tainted by publicity from a class action suit.

Table 3. Main meta-analysis and sensitivity analyses conducted on the association between ever regular use of talcum powder products in the perineal area and ovarian cancer (all types combined).

Studies in meta-analysis	N*	RR-estimate				Heterogeneity	
		Meta-RR	95% CI		p-value	I ²	p-value
<i>Main Meta-Analysis - list in Figure 1 Forest plot</i>	21	1.28	1.19	1.38	0.00	32.9	0.07
<i>Sensitivity analyses</i>							
Substitute Gates 2008 for Gates 2010	21	1.30	1.21	1.40	0.00	22.9	0.16
Substitute Schildkraut B for Schildkraut A	21	1.27	1.17	1.37	0.00	30.8	0.08
Add Shushan	22	1.29	1.19	1.39	0.00	33.8	0.06
Substitute List A** for Terry	27	1.27	1.19	1.35	0.00	26.2	0.10
Substitute List A for Terry and Gates 2008 for Gates 2010	27	1.29	1.21	1.37	0.00	16.6	0.22
Substitute List A for Terry and Schildkraut B for Schildkraut A	27	1.26	1.18	1.34	0.00	24.5	0.12
Substitute List A for Terry and add Shushan	28	1.28	1.20	1.36	0.00	27.4	0.09

*N: Number of RRs that went into the meta-analysis. This is not synonymous with the number of studies because some RRs (e.g. Terry 2013, Cramer 2016) embody multiple studies.

**List A studies: Cramer 2016; Wu 2015; Terry-Aus 2013; Terry-DOV 2013; Terry-Haw 2013; Terry-HOP 2013; Terry-NCO 2013; Terry SON 2013

Table 4. Comparison of results of three contemporaneous and independent meta-analyses of the association between ever regular use of talcum powder products in the perineal area and ovarian cancer.

Meta-analysis author	N*	Meta-RR	95% CI	Heterogeneity p-value
Siemiatycki 2018	21	1.28	1.19-1.38	0.07
Berge 2018	27	1.22	1.13-1.30	0.02
Penninkilompi 2018	26	1.35	1.24-1.39	0.31

* Number of published RR estimates that went into the meta-analysis. This does not necessarily correspond to the number of studies, since, for example, the Terry 2013 pooled estimate used in the Siemiatycki meta-analysis embodied 10 studies.

Table 5. Relative risk estimates between ever regular use of talcum powder products on sanitary napkins and ovarian cancer, and results of meta-analysis.

Author	Number exposed cases	RR ¹	95% CI ²	
Chang 1997	51	1.26	0.81	1.96
Cook 1997	38	0.9	0.5	1.5
Cramer 1999	20	1.45	0.68	3.09
Gertig 2000	32	0.89	0.61	1.28
Harlow 1989	8	2.6	0.9	22.4 ²
Harlow 1992	9	1.1	0.4	2.8
Houghton 2014	93	0.95	0.76	1.20
Ness 2000	77	1.6	1.1	2.3
Rosenblatt 1992	21	4.8	1.3	17.8
Rosenblatt 2011	55	0.82	0.58	1.16
Whittemore 1988	5	0.62	0.21	1.80
Wong 1999	13	0.9	0.4	2.0
Meta-analysis		1.08	0.89	1.31
p-value for heterogeneity = 0.09				

1. RR or OR.
2. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.

Table 6. Relative risk estimates between subgroups defined by cumulative exposure measures¹ and ovarian cancer², from various studies.

Author	Cumulative applications ³	Number exposed cases	RR ⁴	95% C.I.	
Cook 1997 ⁴	< 2000	20	1.8	0.9	3.5
	2001-5000	24	1.6	0.9	2.9
	5001-10000	21	1.2	0.6	2.4
	>10000	28	1.8	0.9	3.4
Harlow 1992	<1000	18	1.3	0.7	2.7
	1000-10000	54	1.5	0.9	2.4
	>10000	42	1.8	1.0	3.0
Mills 2004	Quartile 1	18	1.0	0.6	1.8
	Quartile 2	28	1.8	1.1	3.0
	Quartile 3	34	1.7	1.1	2.7
	Quartile 4	20	1.1	0.6	1.8
	10000+	18	0.87	0.48	1.57
Schildkraut 2016	≤3600	92	1.16	0.83	1.63
	>3600	152	1.67	1.23	2.26
Terry 2013 ⁵	Quartile 1	534	1.14	1.00	1.31
	Quartile 2	541	1.23	1.08	1.41
	Quartile 3	542	1.22	1.07	1.40
	Quartile 4	586	1.32	1.16	1.52

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a cumulative measure. All of these were case control studies.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. For the Cook study the metric was the number of days on which the woman had ever applied the powder. For the other studies the metric is based on an estimate of the total number of applications.

4. RR or OR.
5. This study was based on a pooling of studies from 8 teams. Two of the teams (Cramer 2016 and Rosenblatt 2011) published separate analyses of risk by cumulative number of applications. But these are not shown here because they are rendered redundant by the Terry 2013 pooled results.

Table 7. Relative risk estimates between subgroups defined by duration of use¹ and ovarian cancer², from various studies.

Author	Duration of use	Number exposed cases	RR ⁴	95% C.I.	
Chang 1997	<30	60	1.7	1.1	2.6
	30-40	71	1.4	1.0	2.2
	>40	41	0.9	0.5	1.4
Cramer 1999	<20 years	55	1.9	1.2	3.0
	20-30 years	32	1.3	0.8	2.3
	>30 years	59	1.4	0.9	2.3
Cramer 2016	< 8 years of use	133	1.31	1.03	1.68
	8-19 years of use	126	1.31	1.02	1.68
	20-35 years of use	147	1.35	1.07	1.70
	>35 years of use	129	1.33	1.03	1.71
Harlow 1992	<10 years	14	1.2	0.5	2.6
	10-29 years	49	1.6	1.0	2.7
	> 30 years	51	1.6	1.0	2.7
Houghton 2014	<9 years	135	1.09	0.88	1.36
	10+ years	97	1.02	0.80	1.30
Ness 2000	<1 year	17	2.0	1.0	4.0
	1-4 years	76	1.6	1.1	2.3
	5-9 years	40	1.1	0.8	1.9
	>10 years	233	1.2	1.0	1.5
Mills 2004	<3 years	18	1.0	0.6	1.8
	4-12 years	32	1.9	1.2	3.0
	13-30 years	29	1.5	0.9	2.3
	>30 years	21	1.2	0.7	2.1

Author	Duration of use	Number exposed cases	RR ⁴	95% C.I.	
Rosenblatt 2011	1-9 years	33	1.39	0.85	2.28
	10-19 years	29	1.46	0.87	2.45
	20-34 years	30	1.28	0.78	2.10
	35+ years	19	0.91	0.51	1.62
Schildkraut 2016	≤20 years	101	1.33	0.95	1.86
	>20 years	144	1.52	1.11	2.07
Whittemore 1988	1-9 years	34	1.6	1.0	2.6
	10+	50	1.1	0.7	1.7
Wong 1999	1-9 years	39	0.9	0.6	1.5
	10-19 years	49	1.4	0.9	2.2
	>20 years	101	0.9	0.6	1.2
Wu 2015	Per 5 years of exposure	1273	1.14	1.09	1.20

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of duration.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR.

Table 8. Relative risk estimates between subgroups defined by measures of frequency of use¹ and ovarian cancer², from various studies.

Author	Frequency of use	Number exposed cases	RR ⁴	95% C.I.	
Booth 1989	Rarely	6	0.9	0.3	2.4
	Monthly	7	0.7	0.3	1.8
	Weekly	57	2.0	1.3	3.4
	Daily	71	1.3	0.8	1.9
Chang 1997	<10 per month	76	1.8	1.2	2.7
	10-25 per month	54	1.1	0.7	1.7
	Per 10 applications per month		0.9	0.7	1.1
Cramer 1999	<30 per month	64	2.2	1.4	3.6
	30-39 per month	59	1.7	0.8	1.8
	≥40 per month	23	1.7	0.8	3.1
Cramer 2016	1-7 days per month	220	1.17	0.96	1.44
	8-29 days per month	110	1.37	1.05	1.78
	>30 days per month	205	1.46	1.20	1.78
Gates 2008	<1 per week	18	0.98	0.54	1.79
	1-6 per week	22	1.01	0.57	1.79
	Daily	35	1.44	0.88	2.37
Harlow 1992	<5 per month	32	1.5	0.8	2.7
	5-29 per month	24	1.2	0.6	2.2
	≥30 per month	58	1.8	1.1	3.0

Author	Frequency of use	Number exposed cases	RR ⁴	95% C.I.	
Mills 2004	<1 per week	34	1.3	0.9	2.1
	1-3 per week	31	1.6	0.7	1.8
	4-7 per week	41	1.7	1.1	2.6
Schildkraut 2016	<Daily	88	1.12	0.80	1.58
	Daily	158	1.71	1.26	2.33
Whittemore 1988	1-20 per month	41	1.3	0.8	2.0
	>20 per month	44	1.5	0.9	2.2

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of frequency of use.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR

Table 9. Relative risk estimates between ever regular use of talcum powder products¹ in the perineal area and invasive serous ovarian cancer, from various studies.

Author	Number exposed cases	RR ²	95% CI ³	
Cook 1997	71	1.7	1.1	2.5
Gates 2010	131 ⁴	1.06	0.84	1.35
Harlow 1992	60	1.4	0.9	2.2
Houghton 2014	105	1.13	0.84	1.51
Mills 2004	42	1.77	1.12	2.81
Schildkraut 2016	165	1.38	1.03	1.85
Terry 2013	1197	1.24	1.13	1.35
Wong 1999	136	1.2	0.7	2.1
Meta-analysis		1.25	1.15	1.36
p-value for heterogeneity 0.06				

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. RR or OR.
3. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
4. Estimated based on Table 1 of Gates 2010.

Table 10. Some major misconceptions in reviewing evidence on talc and ovarian cancer

1. Cohort studies are more valid and informative than case-control studies.
2. Hospital-based case-control studies are more valid and informative than the population-based case-control studies.
3. Counting the number of “statistically significant” results is a valid way of assessing the consistency of results among multiple studies.
4. If a product has been used for a long time, it must be safe
5. You cannot prove causality with an RR less than 2.0.
6. Government agencies provide a reliable up-to-date source of scientific information.
7. A biological mechanism must be proven before we can establish causality
8. Bradford-Hill “aspects” represent a recipe list of necessary ingredients.

Table 11. Selected examples of some of the recognized causal associations that have RR less than 2.0

Agent	Disease	Approximate RR
Urban air pollution	Lung cancer	1.09 ¹
Trichloroethylene	Kidney cancer	1.32 ²
Diesel engine emissions	Lung cancer	1.42 ³
Benzene	Leukemia	1.72 ⁴
Domestic radon gas	Lung cancer	1.29 ⁵
Second hand cigarette smoke	Lung cancer	1.64
Intermittent intense sun exposure	Melanoma of the skin	1.61 ⁶
Estrogen-progestin menopausal therapy	Breast cancer	1.59 ⁷

¹ Hamra GB, Guha N, Cohen A, et al (2014). Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis, *Environ Health Perspect* 122:906-911.

² Karami S, Lan Q, Rothman N, et al (2012). Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occupational and Environmental Medicine* 69:858-867.

³ Mahjub H, Sadri G (2006). Meta-analysis of case-referent studies of specific environmental or occupational pollutants on lung cancer. *Indian Journal of Cancer* 43(4):169-173.

⁴ Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ (2010). Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environmental Health* 9(31):1-8.

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Report on talcum powder use and ovarian cancer

Jack Siemiatycki

Cigarette smoking	Cardiovascular disease	1.6 ⁸
Physically inactive (compared with physically active) ⁹	Hypertension	1.19
	Diabetes	1.12
Low fruit and vegetable diet	Cardiovascular disease	1.09 ¹⁰

⁸ Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on British male doctors, *British Medical Journal*, 328(7455):1519.

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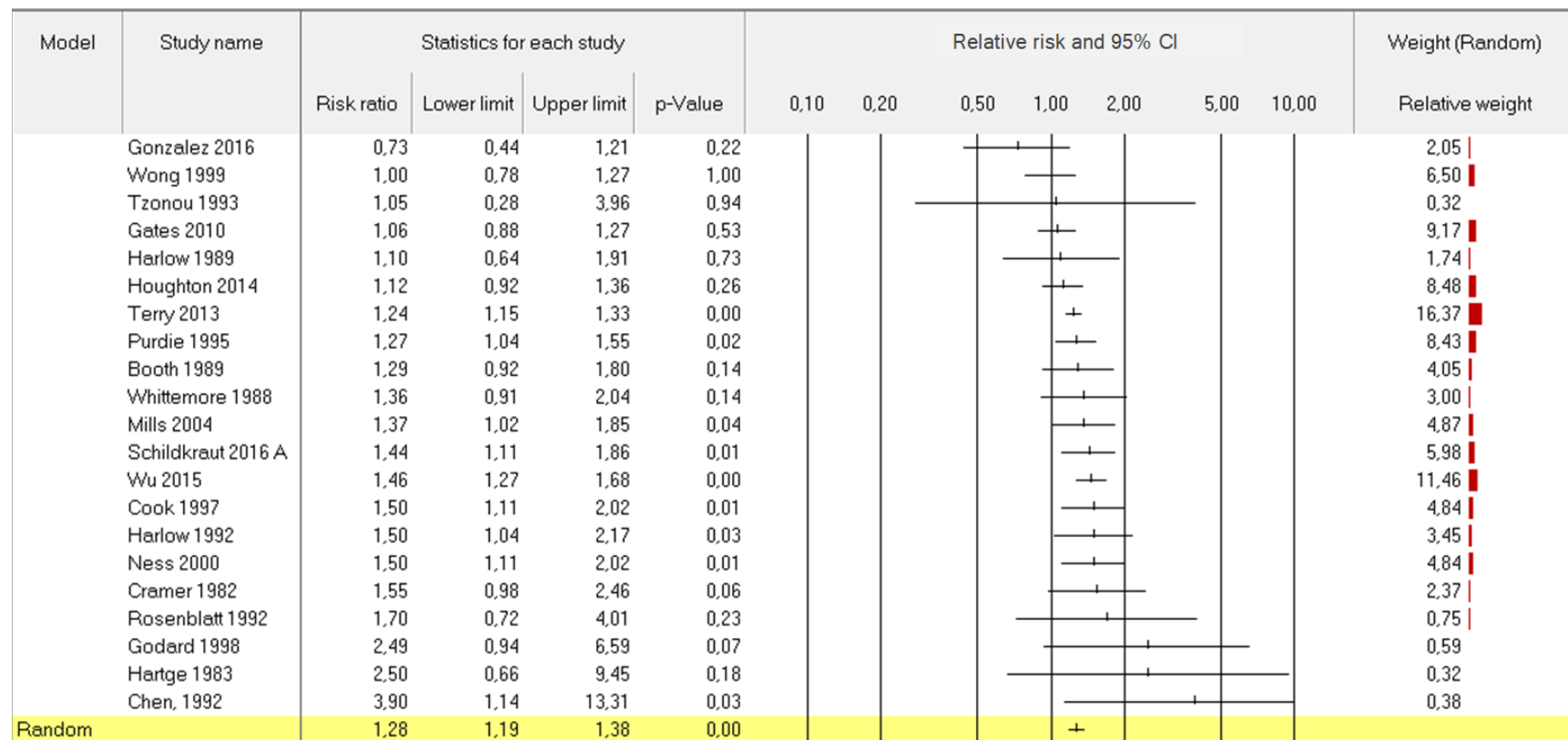
¹⁰ Aune D, Giovannucci E, Boffetta P, Fadnes L, Keum N, Norat T, Greenwood D, Riboli E, Vatten L, Tonstad S (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies, *International Journal of Epidemiology* 43(3):1029-1056. (This RR estimate is computed from the reciprocal of the High fruit and vegetable variable that was reported by the authors. That is, 1/0.92).

Table 12. Bradford Hill aspects in relation to perineal talc exposure and ovarian cancer

Aspect	Brief comment	Weight in evaluating causality
Strength of the association	There are stronger associations and there are weaker associations	High
Dose response relationship	Reasonably clear increase in risk with increasing exposure	High
Consideration of alternative explanations – absence of bias	Yes considered, and none is compelling	High
Replication of the findings	Very strong, almost all studies support association	High
Temporal relationship	Exposure preceded disease in all studies	Moderate
Biological plausibility	There are plausible mechanisms	Moderate
Cessation of exposure	Not applicable.	Less
Specificity of the association	Yes, talc is not associated with a multitude of diseases	Less
Coherence with other knowledge	Could be similar to asbestos carcinogenicity	Less
Analogy		Less

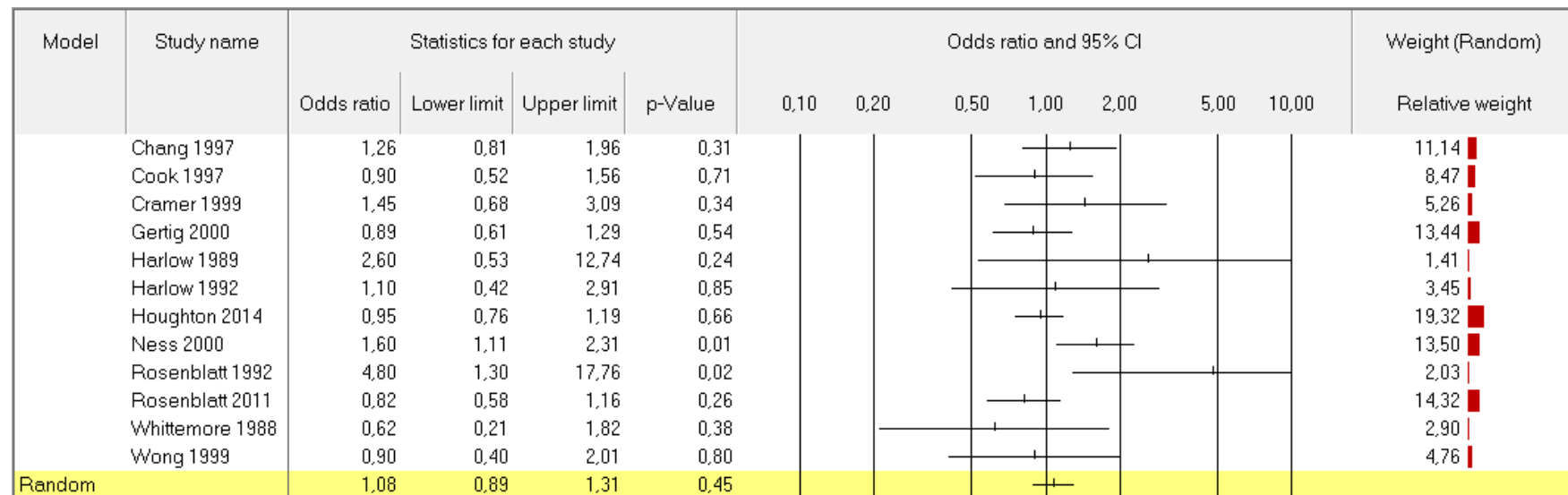
12. Figures

Figure 1. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talc powder in the perineal area, based on all informative studies, studies ordered by magnitude of RR.



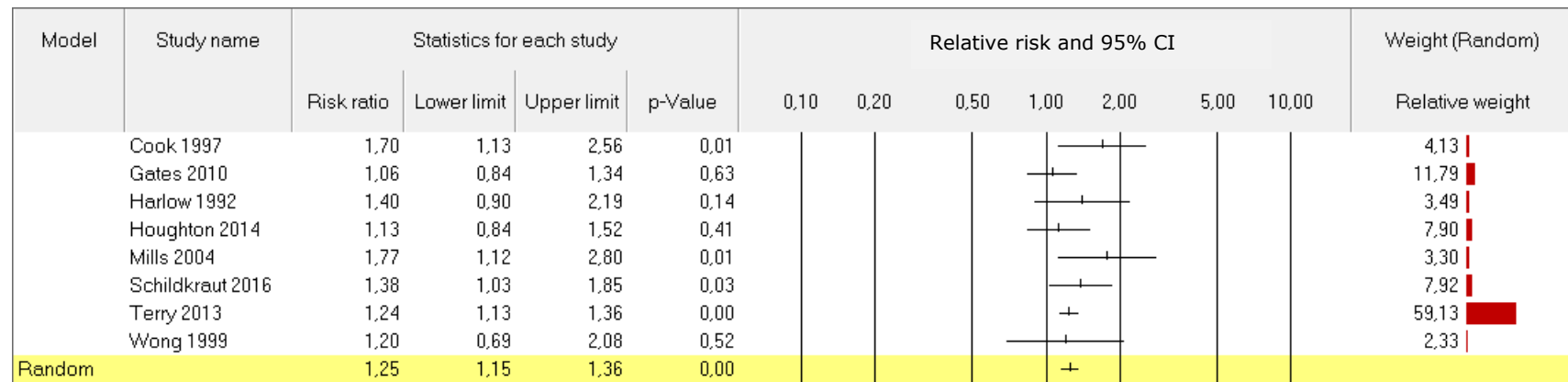
Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	21	1.264	1.204	1.327	9.474	0.000	29.813	20	0.073	32.916	0.008	0.008	0.000	0.088
Random effects	21	1.280	1.186	1.381	6.364	0.000								

Figure 2. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talcum powder products on sanitary napkins, based on all informative studies.



Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	12	1,041	0,911	1,189	0,591	0,554	17,614	11	0,091	37,551	0,037	0,045	0,002	0,193
Random effects	12	1,078	0,888	1,309	0,763	0,445								

Figure 3. Meta-analysis of relative risk of invasive serous ovarian cancer among women who regularly used talcum powder products in the perineal area, based on all informative studies



Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	8	1,250	1,161	1,345	5,963	0,000	7,401	7	0,388	5,422	0,001	0,011	0,000	0,033
Random effects	8	1,254	1,152	1,364	5,249	0,000								

13. Appendix A

Appendix Table A1. Papers that contain some results on the association between exposure to perineal talc and ovarian cancer, and whether the paper was included in my meta-analyses of the binary Ever/Never exposed variable

Author	Included/excluded	Reasons for exclusion
Booth 1989	Core Inclusion	
Chang 1997	Core Inclusion	
Chen 1992	Core Inclusion	
Cook 1997	Core Inclusion	
Cramer 1982	Core Inclusion	
Cramer 1995	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 1999	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2005	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2016	Excluded when Terry 2013 is included	Considerable overlap between this and the Terry 2013 NEC component
Eltabbakh 1998	Excluded	Cases were peritoneal cancer and controls were ovarian cancer
Gates 2008 ²	Included in one sensitivity analysis	Overlap with Gates 2010

Author	Included/excluded	Reasons for exclusion
Gates 2010 ²	Included in all analyses except one sensitivity analysis	This may be a more complete analysis than Gates 2008, but the degree of overlap is unclear.
Gertig 2000	Excluded	Subsumed in Gates 2008 and Gates 2010
Godard 1998	Core inclusion	
Gonzalez 2016	Core inclusion	
Green 1997	Excluded	This appears to be an analysis of a subset of the subjects in Purdie 1995
Hankinson 1993	Excluded	Numerical results were not presented.
Harlow 1989	Core inclusion	
Harlow 1992	Core inclusion	
Hartge 1983	Core inclusion	
Houghton 2014	Core inclusion	
Jordan 2007	Excluded	Benign tumours only
Kurta 2012	Excluded	Included in Terry 2013
Langseth 2004	Excluded	Not based on perineal application of cosmetic powder.
Lo-Ciganic 2012	Excluded	Same study as Kurta 2012 and included in Terry 2013.
Merrit 2008	Excluded	Included in Terry 2013

Author	Included/excluded	Reasons for exclusion
Mills 2004	Core inclusion	
Moorman 2009	Excluded	Included in Terry 2013
Pike 2004	Excluded	Included in Terry 2013
Purdie 1995	Core inclusion	
Ness 2000	Core inclusion	
Rosenblatt 1992	Core inclusion	
Rosenblatt 2011	Core inclusion	
Schildkraut 2016	Core inclusion	
Shushan 1996	Included in sensitivity analysis	Unclear on how they obtained data on talc exposure or what the route of exposure was
Terry 2013	Included in Main analysis, but replaced by component studies in sensitivity analyses	
Tzonou 1983	Core inclusion	
Whittemore 1988	Core inclusion	
Wong 1999	Core inclusion	
Wu 2015	Core inclusion	

Appendix Table A2. Some administrative and contextual information on the studies used in the following tables

Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Booth 1989	London, Oxford UK	1978-1983	Case-control; Hospital controls
Chen 1992	Beijing Cancer Registry	1984-1986	Case-control; Population controls
Cook 1997	Washington State	1986-1988	Case-control; Population controls
Cramer 1982	Boston	1978-1981	Case-control; Population controls
Cramer 2016	New England	1992-2008	Case-control; Population controls
Gates 2008 ²	USA – NHS study	1976-2004	Case-control nested in Cohort (US nurses)
Gates 2010 ²	USA – pooled 2 cohorts of nurses NHS and NHSII	1976-2004 1989-2005	Cohort (US Nurses)
Godard 1998	Montreal, Canada	1995-1996	Case-control; Population controls
Gonzalez 2016	Puerto Rico and 11 States USA	2003-2014	Cohort
Harlow 1989	Washington State	1980-1985	Case-control; Population controls
Harlow 1992	Boston	1984-1987	Case-control; Population controls

Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Hartge 1983	Washington, DC	1974-77	Case-control; Population controls
Houghton 2014	USA	1993-2012	Cohort (WHI)
Mills 2004	California	2000-2001	Case-control; Population controls
Ness 2000	Pennsylvania, New Jersey, Delaware	1994-1998	Case-control; Population controls
Purdie 1995	Australia	1990-1993	Case-control; Population controls
Rosenblatt 1992	Baltimore	1981-1985	Case-control; Hospital controls
Schildkraut 2016	USA	2010-2015	Case-control; Population controls
Shushan 1996	Israel	1990-1993	Case-control Population controls
Terry 2013	Pooled 8 studies: USA & Australia	1984-2008	Case-control; Population controls
Terry-AUS 2013	Australia	2002-2006	Case-control Population controls
Terry – DOV ³ 2013	Washington State	2002-2009	Case-control Population controls
Terry – HAW 2013	Hawaii	1993-2008	Case-control Population controls

Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Terry – HOP 2013	Pennsylvania, Ohio, Western NY State	2003-2008	Case-control Population controls
Terry – NCO 2013	North Carolina	1999-2008	Case-control Population controls
Terry – NEC 2013	Massachusetts, New Hampshire	1992-2006	Case-control Population controls
Terry – SON 2013	Southern Ontario	1989-1992	Case-control Population controls
Terry – USC 2013	Los Angeles County	1992-1998	Case-control Population controls
Tzonou 1983	Athens	1989-1991	Case-control; Controls – hospital visitors
Whittemore 1988	San Francisco	1983-1985	Case-control; Hospital & population controls
Wong 1999	Buffalo	1982-1992	Case-control; Hospital controls
Wu 2015	Los Angeles County	1992-2008	Case-control; Population controls
1.	Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.		
2.	The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.		
3.	Terry – DOV 2013: the information in Terry 2013 is updated information included in Rosenblatt 2011.		

Appendix Table A3. Covariates used in the analyses and exposure variables in the studies used in the following tables.

Author	Exposure variable selected	Covariates used in analysis
Booth 1989	At least monthly use	Since the authors did not present results for “ever” exposed, I calculated the OR from crude numbers in their tables. Therefore the OR presented is a crude one. However, results presented in Table 7 adjusted for age and social class
Chen 1992	Dusting perineum or lower abdomen > 3 months	Education
Cook 1997	Lifetime perineal application	Age
Cramer 1982	Any use as dusting powder and/or on sanitary napkins	Parity; menopausal status
Cramer 2016	Any talc use	Age; study center (MA, NH); BMI; primary relative with breast or ovarian cancer; parity; OC use; tubal ligation
Gates 2008 ¹	Regular genital talc use (1 per week or more)	Age; OC ² use; parity; BMI; post-menopausal hormone use
Gates 2010 ¹	Regular genital talc use (1 per week or more)	Age; BMI; physical activity; smoking; family history of breast or ovarian ca; OC use; tubal ligation; hysterectomy; age menopause; estrogen use
Godard 1998	Ever use of talc on perineum	Age; reproductive factors; OC use; tubal ligation; alcohol use; breast and abdominal surgery
Gonzalez 2016	Talc use in the past 12 months	Race; body mass index; parity; duration of oral contraceptive use; baseline menopause status; and patency

Author	Exposure variable selected	Covariates used in analysis
Harlow 1989	Any genital talc use	Age; county; parity; OC use
Harlow 1992	Any genital talc use	Age; county; parity; marital status; education; religion; weight; use of sanitary napkins; douching
Hartge 1983	Any genital talc use	Race; age; gravidity
Houghton 2014	Combined use: longest duration of use among the applications to genitals, sanitary napkins and diaphragms	Age; race; OC use; HRT ³ use; family history of ovarian ca; age at last birth; BMI; smoking; tubal ligation; parity
Mills 2004	Ever use of talcum powder in genital area	Age; race/ethnicity; OC use; breast-feeding
Ness 2000	Genital rectal talc use	Age; parity; family history of ovarian ca;
Purdie 1995	Ever used talc in perineal region	Age; parity; duration of OC use; education; BMI; smoking; family history of ovarian ca
Rosenblatt 1992	Ever use of bath talc	Number of live births
Schildkraut 2016	Regular use of talc, cornstarch, baby or deodorising powder – at least once a month for 6 months	Age at diagnosis/interview; study site; education; tubal ligation; parity; BMI duration of OC use first degree family history of breast or ovarian cancer; and interview year
Shushan 1996	Talc use – never, seldom, moderate, a lot	Crude OR

Author	Exposure variable selected	Covariates used in analysis
Terry 2013 – all components of the pooled analysis	Genital powder use	Age; OC use; parity; BMI; tubal ligation; ethnicity; race; tubal ligation; hysterectomy; breastfeeding
Tzonou 1983	Ever use of talc in perineal region	Age; years of schooling; weight before onset of the disease; age at menarche; menopausal status and age at menopause; parity and age at first birth; tobacco smoking; coffee drinking; consumption of alcoholic beverages; hair dyeing; use of analgesics and tranquilizers/hypnotics
Whittemore 1988	Talcum powder used on any two of perineum, sanitary pads and diaphragm	Age; race; hospital; parity
Wong 1999	Ever use of talc on genital region or thighs	Age; income; education; geographic location; OC use; smoking; family history of ovarian ca; age at menarche; menopausal status; tubal ligation or hysterectomy
Wu 2015	Genital talc use >1 year	Age; race/ethnicity; interviewer; reproductive variables; sociodemographic variables; medical history; hormonal variables; BMI.
1.	The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.	
2.	OC: oral contraceptive	
3.	HRT: hormone replacement therapy	

14. Appendix B

Comparison of studies used and results extracted from articles referenced in three different meta-analyses.*

Penninkilampi 2018 Study / RR(95%CI)	Berge 2018 Study / RR(95%CI)	Siemiatycki 2018 Study / RR(95%CI)
Booth 1989 1.30 (0.94-1.80)	<i>Booth 1989</i> <i>1.29 (0.92 - 1.80)</i>	<i>Booth 1989</i> <i>1.29 (0.92 - 1.80)</i>
Chang 1997 1.42 (1.08 – 1.86)	Chang 1997 1.35 (1.03 - 1.76)	
Chen, 1992 3.90 (1.43 – 10.60)	<i>Chen, 1992</i> <i>3.90 (0.91 - 10.60)</i>	<i>Chen, 1992</i> <i>3.90 (0.91 - 10.60)</i>
<i>Cook 1997</i> <i>1.50 (1.11 – 2.02)</i>	<i>Cook 1997</i> <i>1.50 (1.10 - 2.00)</i>	<i>Cook 1997</i> <i>1.50 (1.10 - 2.00)</i>
Cramer 1982 1.60 (1.21 – 2.12)	<i>Cramer 1982</i> <i>1.92 (1.27 - 2.89)</i>	<i>Cramer 1982</i> <i>1.92 (1.27 - 2.89)</i>
Cramer 2016 1.42 (1.03 – 1.95)	Cramer 2016 1.32 (1.14 - 1.50)	Cramer 2016 1.33 (1.16 – 1.52)
		Gates 2008 1.24 (0.83 - 1.83)
	<i>Gates 2010</i> <i>1.06 (0.89 - 1.28)</i>	<i>Gates 2010</i> <i>1.06 (0.89 - 1.28)</i>
Gertig 2000 1.09 (0.86 – 1.38)		

Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
<i>Godard 1998</i> <i>2.49 (0.94 - 6.58)</i>	<i>Godard 1998</i> <i>2.49 (0.94 - 6.58)</i>	<i>Godard 1998</i> <i>2.49 (0.94 - 6.58)</i>
<i>Gonzalez 2016</i> <i>0.73 (0.44 - 1.20)</i>	<i>Gonzalez 2016</i> <i>0.73 (0.44 - 1.20)</i>	<i>Gonzalez 2016</i> <i>0.73 (0.44 - 1.20)</i>
	Goodman 2008 0.99 (0.7 - 1.41)	
Green 1997 1.30 (1.06 - 1.60)		
Harlow 1989 1.10 (0.58 - 2.10)	<i>Harlow 1989</i> <i>1.10 (0.70 - 2.10)</i>	<i>Harlow 1989</i> <i>1.10 (0.70 - 2.10)</i>
	<i>Harlow 1992</i> <i>1.50 (1.00 - 2.10)</i>	<i>Harlow 1992</i> <i>1.50 (1.00 - 2.10)</i>
<i>Hartge 1983</i> <i>2.50 (0.66 - 9.45)</i>	<i>Hartge 1983</i> <i>2.50 (0.70 - 10.00)</i>	Hartge 1983 0.70 (0.40 - 1.10)
<i>Houghton 2014</i> <i>1.12 (0.92 - 1.36)</i>	Houghton 2014 1.06 (0.87 - 1.28)	<i>Houghton 2014</i> <i>1.12 (0.92 - 1.36)</i>
Kurta 2012 1.40 (1.16 - 1.69)		
	Lo-Ciganic 2012 1.34 (1.07 - 1.66)	

Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
Merritt 2008 1.17 (1.01 – 1.36)	Merritt 2008 1.13 (0.92 - 1.38)	
<i>Mills 2004</i> 1.37 (1.02 - 1.85)	<i>Mills 2004</i> 1.37 (1.02 - 1.85)	<i>Mills 2004</i> 1.37 (1.02 - 1.85)
	Moorman 2009 1.37 (1.05 - 1.8)	
<i>Ness 2000</i> 1.50 (1.10 - 2.02)	<i>Ness 2000</i> 1.50 (1.10 - 2.00)	<i>Ness 2000</i> 1.50 (1.10 - 2.00)
<i>Purdie 1995</i> 1.27 (1.04 - 1.54)	<i>Purdie 1995</i> 1.27 (1.04 - 1.54)	<i>Purdie 1995</i> 1.27 (1.04 - 1.54)
Rosenblatt 1992 1.70 (0.72 – 4.01)	<i>Rosenblatt 1992</i> 1.70 (0.70 - 3.90)	<i>Rosenblatt 1992</i> 1.70 (0.70 - 3.90)
Rosenblatt 2011 1.27 (0.97 – 1.66)	Rosenblatt 2011 1.13 (0.93 - 1.36)	
<i>Schildkraut 2016</i> 1.44 (1.11 - 1.86)	<i>Schildkraut 2016</i> 1.44 (1.11 - 1.86)	<i>Schildkraut 2016 A</i> 1.44 (1.11 - 1.86)
		Schildkraut 2016 B 1.19 (0.87 - 1.63)
Shushan 1996 2.00 (1.11 – 3.60)		Shushan 1996 1.97 (1.06 – 3.66)

Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
		Terry 2013 1.24 (1.15 - 1.33)
<i>Tzonou 1993</i> <i>1.05 (0.28 - 3.96)</i>	<i>Tzonou 1993</i> <i>1.05 (0.28 - 3.98)</i>	<i>Tzonou 1993</i> <i>1.05 (0.28 - 3.98)</i>
Whittemore 1988 1.40 (0.98 – 2.00)	<i>Whittemore 1988</i> <i>1.36 (0.91 - 2.04)</i>	<i>Whittemore 1988</i> <i>1.36 (0.91 - 2.04)</i>
Wong 1999 0.92 (0.24 – 3.57)	<i>Wong 1999</i> <i>1.00 (0.80 - 1.30)</i>	<i>Wong 1999</i> <i>1.00 (0.80 - 1.30)</i>
Wu 2015 1.32 (1.14 – 1.52)	<i>Wu 2015</i> <i>1.46 (1.27 - 1.69)</i>	<i>Wu 2015</i> <i>1.46 (1.27 - 1.69)</i>

- * When two or three of the meta-analyses extracted the identical results from the source paper, it is indicated with italic characters.

15. Appendix C

Examples of historic discoveries made on the basis of empirical observation of an association, without the existence of a validated biological mechanism of action.

- Jenner (18th century) discovered that smallpox could be prevented by “vaccinating” people. This was based on observation of the effect of exposure to cowpox. He had no idea about viruses or the biology of smallpox. He only knew that the “association” he observed between vaccination and the prevention of smallpox was so strong as to convince him it was causal. Millions of lives were saved as a result.
- Snow (19th century) discovered that cholera was caused by something in the water supply. He did not know what the pathogen was or how it produced the disease, but he showed with sufficient epidemiologic proof that drinking water from a polluted source produced much higher rates than drinking water from a clean source. Despite the ignorance of biological mechanisms, the public health authorities acted on his findings and thereby greatly reduced the incidence of cholera.
- Rheumatic fever and rheumatic heart disease were quite common causes of disease and death, striking relatively young people. For many decades it was recognized that there was an association between infection with the streptococcus bacterium and rheumatic heart disease, but it was not understood how the bacterium could have such an effect. The lack of understanding of the biological mechanisms did not get in the way of prevention of rheumatic heart disease by preventing and treating streptococcus infection.
- In the 1930's and 1940's, it was noticed that communities with high natural levels of fluoride in the water had much lower levels of dental caries than communities with low fluoride levels. Additional observational research confirmed the clear causal relationship and this led to extensive use of fluoride in various ways to reduce dental disease. But, all this occurred

before the mechanisms by which fluoride acted on teeth were understood. And, indeed the mechanisms are still not fully understood.

- In the late 1940's and early 1950's, evidence was accumulating that cigarette smokers had higher rates of lung cancer than non-smokers. This "association" was ridiculed at the time, among other reasons, because there was no proven biological mechanism. Attempts to replicate smoking-related lung cancer incidence in laboratory animals were largely unsuccessful. Nor was there a deep understanding of the cellular processes that allow the inhalation of cigarette smoke to culminate in a tumor. Scores of studies later and many decades later, the outlines of a credible biological mechanism began to emerge. The absence of a proven biological mechanism did not hinder the US Surgeon General and other national bodies from concluding that there was a causal link as early as the 1960's.
- Many chemicals have been found to be carcinogenic as a result of epidemiologic studies among workers. Examples of these are asbestos, silica, nickel compounds, chromium compounds, benzene, and others. Some of these discoveries go back to the first half of the 20th century, and, for most of them, many decades passed between the time they were recognized as carcinogens, on the basis of epidemiologic associations, and the elaboration of credible mechanisms of how they induce cancer. (Siemiatycki 2015) Most known carcinogens were first discovered empirically by medical doctors or epidemiologists, usually as part of large data collection activities or just plain astute observation on the part of medical doctors.

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David Steinberg, CV

David Steinberg publications list

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17, 2018, Nov. 5, 2018)

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Weed, Douglas. A Report Regarding General Causation and an Evaluation of the Reliability and Validity of the Plaintiffs' Experts' Reports Designated for the Plaintiff, Lori Oules (Feb. 1, 2017)

17. Curriculum Vitae – Jack Siemiatycki

CURRICULUM VITAE

Jack Siemiatycki

TABLE OF CONTENTS

STATISTICAL SUMMARY OF SELECTED ACCOMPLISHMENTS	2
GENERAL INFORMATION.....	3
EDUCATION.....	3
CURRENT ACADEMIC APPOINTMENTS.....	3
PREVIOUS ACADEMIC APPOINTMENTS AND WORK EXPERIENCE.....	3
SIGNIFICANT INTERNAL ADMINISTRATIVE APPOINTMENTS.....	3
SIGNIFICANT INSTITUTIONAL COMMITTEES.....	4
CURRENT MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES (INVITED).....	4
PAST MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES, CONSULTATIONS (INVITED)	4
OTHER SIGNIFICANT EXTERNAL CONSULTATIONS (INVITED).....	6
HONOURS.....	9
GRANT REVIEW, JOURNAL REVIEW AND PERSONNEL REVIEW	9
Associate Editor.....	9
Contributing Editor.....	9
Chairman of grant review panels.....	9
Member of grant review panels.....	9
External referee for tenure or promotion of personnel in other institutions	9
THESES	10
ARTICLES PUBLISHED PEER REVIEW	10
BOOK CHAPTERS (invited) AND IARC MONOGRAPHS.....	23
PUBLICATIONS WITHOUT PEER REVIEW, OTHER SCIENTIFIC REPORTS	24
BOOK.....	27
ARTISTIC WORKS.....	27
SCIENTIFIC PRESENTATIONS - INVITED	27
SCIENTIFIC PRESENTATIONS - OFFERED AND ACCEPTED	35
GRANTS AND CONTRACTS RECEIVED	46

STATISTICAL SUMMARY OF SELECTED ACCOMPLISHMENTS

Publications in peer-reviewed journals	245
Book chapters, IARC Monographs	20
Other publications, reports	42
Book (authored)	1
Invited presentations	173
Conference presentations, posters, abstracts : offered and accepted	181
Grants received as P.I. (number)	36
Grants received as P.I. (\$)	\$15.4M
Grants received as co-investigator (number)	59
Grants received as co-investigator (\$)	\$27.9M
H-factor (google scholar)	64
Instances of participation on expert panels, committees, boards of directors, at invitation of governments or public health agencies or research agencies or universities	126
Grant review panels or referee for external institution or journal editorial boards	65
Honours	several

GENERAL INFORMATION

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Fax: (514) 412-7106
E-mail: j.siemiatycki@uMontréal.ca

EDUCATION

1967 B.Sc. (mathematics); McGill University
1970 M.Sc. (mathematical statistics); McGill University
1976 Ph.D. (epidemiology and medical statistics); McGill University
1977 Post-doctoral (cancer epidemiology); International Agency for Research on Cancer, Lyon

CURRENT ACADEMIC APPOINTMENTS

Professor, Department of Social and Preventive Medicine, Université de Montréal (since 2001)
Cancer Research Society-Guzzo Research Chair in Environment and Cancer, Université de Montréal (since November 2007)
Adjunct Professor, Department of Epidemiology, Biostatistics and Occupational Health, McGill University. (since 1979)
Fellow, Canadian Academy of Health Sciences (since 2008)

PREVIOUS ACADEMIC APPOINTMENTS AND WORK EXPERIENCE

1967-71 Research Fellow; Department of Epidemiology and Health, McGill University.
1970-72 Research Director; Pointe St. Charles Community Clinic, Montréal.
1978 Consultant; International Agency for Research on Cancer, Lyon.
1978-2001 Assistant, then Associate (1979), then full Professor (1983):
Epidemiology Research Center, Institut Armand-Frappier, Laval, Québec.
1982-1986 Associate member, McGill Cancer Center, McGill University.
1996-1997 Visiting Scientist. International Agency for Research on Cancer, Lyon.
2001-2015 Canada Research Chair (Tier 1), Université de Montréal (resigned 2011).
2003-2009 Affiliate Scientist. McLaughlin Centre for Pop'n Health Risk Assessment, Univ of Ottawa.

SIGNIFICANT INTERNAL ADMINISTRATIVE APPOINTMENTS

1982-86 Director, Équipe associée de l'Institut de Recherche en Santé et Sécurité du Travail sur les cancers professionnels (affiliated research team of the Quebec Institute for Occupational Health and Safety on Occupational Cancer).
1988-91 Director, Epidemiology Research Center, Institut Armand-Frappier.
1990-98 Director, Équipe prioritaire de recherche en épidémiologie environnementale du FRSQ. (Priority research team in environmental epidemiology)
1998-2001 Member, Governing Council (Conseil d'administration). Institut national de la recherche scientifique, Université du Québec.
2000-2007 Coordinator. Program of Research in Environmental Epidemiology of Cancer (PREECAN), a national program funded by the National Cancer Institute of Canada.
2002-2005 Associate Director for Population Health Sciences, Research Center of the University of Montréal Hospital Center.

- 2006-2007 Director, Epidemiology program, PhD public health, Université de Montréal.
2006-2014 Director, Axe risques à la santé (Health Risks Division). Centre de recherche du Centre hospitalier de l'Université de Montréal.

SIGNIFICANT INSTITUTIONAL COMMITTEES

- 1979-80 Member of faculty committee to negotiate a collective agreement with the Institut Armand-Frappier administration.
1982-92 Member, Research Council. Institut Armand-Frappier.
1998-2001 Member, Institutional advisory council. Institut Armand-Frappier. Institut national de la recherche scientifique
2002-2006 Comité de direction. Centre de recherche du CHUM
2002-2017 Member, Various committees of the Dept Med Soc et Preventive, including Promotions, and Recruitment.
2006-2009 Member, Various committees established to set up a new School of Public Health at l'Université de Montréal
2006-2014 Comité Scientifique de la Recherche du CHUM.

CURRENT MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES (INVITED)

1. Chair of Scientific Advisory Committee of CONSTANCES, a large prospective cohort established in France, under aegis of INSERM, Ministère de la Santé, and other agencies. Since 2011.
2. Member of Comité national d'épidémiologie en cancérologie. Ministère de la Santé et des Services sociaux, Quebec. Since 2014.
3. Member, Advisory committee to Directors of Cartagene, a Quebec population cohort.

PAST MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES, CONSULTATIONS (INVITED)

1. Expert consultative committee to Commission de la santé et sécurité du travail du Québec on the epidemiologic function of the CSST. 1979-80.
2. President of Organizing Committee of Annual Congress of Quebec Public Health Association, Montréal. 1982.
3. Consultative committee of International Agency for Research on Cancer on feasibility of SEARCH programme. 1982.
4. Canadian representative. International Joint Commission (U.S. and Canada) Committee on the Assessment of Human Health Effects of Great Lakes Water Quality. 1982-89.
5. Task Force on Chemicals in the Environment and Human Reproduction Effects in New Brunswick. 1983-85.
6. Chairman and organizer of international workshop sponsored by International Agency for Research on Cancer, Lyon, on use of job exposure information in cancer case-control studies. 1984.
7. Quebec Government Consultative Committee on Alachlor. 1985-86.
8. Chairman and organizer of the International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health, Scarborough, March 1988. 1986-88.
9. Priority Substances Advisory Panel. Panel established under terms of Canadian Environmental Protection Act by Health and Welfare Canada. 1988.
10. Working Group on Electromagnetic Fields under auspices of Health Effects Institute. 1991.
11. Consultative Committee on Environment-related Cancer Surveillance, LCDC, Health and Welfare Canada. 1993-1996.
12. Consultative Committee on an Investigation of Lung Cancer and Environmental Tobacco Smoke, Environmental Health Directorate, Health Canada. 1994-1995.
13. Working Group on Evaluation of Carcinogenicity of Carbon Black, Printing Trades and Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 1995.

14. Working Group on Human Cancer Risks associated with Chrysotile Asbestos. World Health Organization (IPCS) Geneva, June 1995.
15. Secretariat on Evaluation of Chemopreventive Effect of Aspirin and Other NSAIDS for Cancer. International Agency for Res. on Cancer, Lyon, Apr. 1997.
16. Chair. Symposium on Health Risks of Water Disinfection By-products. Convened by Health Canada. Ottawa. May 1997.
17. Working Group. Meeting on Species-specificity in response to carcinogens. Monograph Programme. International Agency for Res. on Cancer, Lyon, Nov. 1997.
18. Board of Directors. Canadian Society for Epidemiology and Biostatistics. 1997-1999.
19. Working Group. Evaluation of Carcinogenicity of Various Industrial Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, Feb. 1998.
20. Canadian Coalition on Cancer Surveillance. 1997-2002.
21. External site review panel. U.S. National Cancer Institute Epidemiology Branch. June 1999.
22. Organizing Committee for Medical Research Council Workshop on Privacy of Health Data. 1999-2000.
23. Organizing Committee, EPI2001. Joint North American Congress of Canadian Society for Epidemiology and Biostatistics, Society for Epidemiologic Research, American Public Health Association (Epid) and American College of Epidemiology, Toronto, 14 – 16 June 2001. 1999-2001.
24. Coordinator of national initiative of the public health community to provide guidance on the structures and functioning of the new Canadian Institutes of Health Research. 1999-2000.
25. Organizing Committee. World Congress of the International Epidemiological Association, Montréal, 18-22 August 2002. 2001-2002.
26. President. Canadian Society for Epidemiology and Biostatistics. 2001-2003. Member of Board. 1997-1999.
27. Working Group. Evaluation of Carcinogenicity of Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 2003.
28. Jury of Consensus Conference on risks and benefits of vaccination for hepatitis B. For Minister of Health of France. Organized by INSERM and ANAES. Paris 2003.
29. Public Advisory Panel. Vinyl Council of Canada. 1998-2004.
30. Advisory Panel. U.S. National Cancer Institute Brain Tumor Study. 1998-2003.
31. Scientific Advisory Committee. Boeing/UAW Workers' Health Studies. 1999-2005.
32. Institute Advisory Board. Canadian Institutes for Health Research – Institute of Circulatory and Respiratory Health. 2001-2005.
33. National Occupational Research Agenda (NORA). Joint consultative committee for US National Cancer Institute and US National Institute for Occupational Safety and Health. 2002-2005.
34. Canadian Cancer Surveillance Alliance. Consultative committee of Health Canada, Canadian Cancer Society, Provincial Cancer Registries, Statistics Canada. 2002-2003.
35. Co-president. Organizing Committee of Joint SER-CSEB Congress, Toronto 27-30 June 2005. (2004-2005).
36. Chair. Monograph Program Meeting. International Agency for Research on Cancer (WHO), France. February 2006.
37. Advisory Committee on Research Ethics and Databanks. Quebec Health Research Council (FRSQ). 2003-2011.
38. Board of Directors. American College of Epidemiology. 2003-2006.
39. Board of Directors. National Cancer Institute of Canada. 2003-2007.
40. Member Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2005-2009.
41. Elected Chair. Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2008-2009.
42. Scientific Advisory Council Canadian Partnership Against Cancer 2007-2009.
43. Advisory Committee. Occupational Cancer Research Centre of Ontario. Since 2009.
44. Working Group on Cancer Prevention, CPAC, 2007-2010.

45. Subgroup Chair and Working Group Member. Evaluation of Carcinogenicity of Non-Ionizing Radiation, Radiofrequency Electromagnetic Fields. Monograph Programme. International Agency for Research on Cancer, Lyon May 2011.
46. Member of Scientific Advisory Board of Bordeaux cancer research center SIRIC-BRIO, Bordeaux France. Since 2013.
47. Member of external review panel. Helmholtz Center Munich Research Institute. Germany. July 2011.
48. Conseil Scientifique de l'Institut de Recherche en Santé Publique (IReSP). Under aegis of INSERM and Ministère de la Santé, France. 2004-2009.
49. Adviser and expert witness for legal team conducting a major class action lawsuit against the Canadian tobacco industry. 2007-2014.

OTHER SIGNIFICANT EXTERNAL CONSULTATIONS (INVITED)

1. Consultation with Quebec Ministry of Justice regarding compensation for homeowners who were advised to use formaldehyde-base home insulation - 1983.
2. Invited participant. Workshop convened by the Science Council of Canada on the future of Epidemiology in Canada, Ottawa - 1985.
3. Consultation with Government of Alberta regarding the evaluation of a report alleging significant health impact in the environment of a sour-gas plant - 1985.
4. Consultation with Quebec Ministry of Environment regarding health effects of residency near an abandoned toxic waste site in LaSalle, Quebec - 1987.
5. Invited participant. Workshop convened by Canadian Public Health Association, Environment Canada and Health and Welfare Canada on Environmental Impact Assessment, Ottawa - 1987.
6. Invited participant. Annual workshops convened by Health Protection Branch of Health and Welfare Canada to discuss the role of Canada in the SEARCH programme of the International Agency for Research on Cancer, Ottawa - 1987-1989.
7. Consultation with Quebec Cree Band Council regarding a research proposal to study developmental effects of consuming fish with high mercury levels - 1989.
8. Invited participant. Workshop convened by Ontario Industrial Disease Standards Panel on the use of epidemiologic data in workers' compensation, Toronto - December 1989.
9. Invited participant. Workshop convened by National Academy of Sciences (U.S.) on Carcinogenicity of Complex Mixtures, Tucson, Arizona - Jan 1990.
10. Invited participant. Workshop convened by Laboratory Centers for Disease Control, Health and Welfare Canada on Multiple Chemical Sensitivities, Ottawa - May 1990
11. Member of expert advisory panel to the pan-Canadian case-control study of electromagnetic fields and childhood leukemia. Sponsored by Canadian Electrical Assoc, EPRI (U.S.A.), Health and Welfare Canada. 1990-1996.
12. Organizer of Workshop to Plan a Pan-North American Case-control Study of Lung Cancer. Sponsored by Health and Welfare Canada. Toronto. March 1991.
13. Invited participant. Workshop convened by Environmental Health Directorate of Health and Welfare Canada, on Environmental Epidemiology in Canada. Ottawa. March 1992
14. Invited participant. Workshop convened by Harvard Center for Risk Analysis on implementing a new type of risk assessment. Maryland. April 1992.
15. Member of Technical Advisory Panel for epidemiology studies of foundry workers - CIIT. Research Triangle Park, N.C. Feb. 1993
16. Consultant to Health Effects Institute - Asbestos Research, on Options for Characterizing Worker Activities in Buildings, Boston. Feb. 1993.
17. Advisory panel to Laboratory Centers for Disease Control, Health and Welfare Canada, on Environmental Epidemiology under the Green Plan. March 1993.
18. Member of External Advisory Committee. Champlain Adirondack Biosphere Environmental Health Sciences Center, University of Vermont. 1993.
19. Consultant to Michigan Cancer Foundation on a variety of epidemiologic studies. 1993-1996.

20. Invited to address President Clinton's Panel on Cancer regarding priorities in cancer research. Bethesda, MD. April 1994.
21. Invited participant. Science and Technology Review Consultation. Government of Canada. Montréal. September 1994.
22. Invited participant. Strategic planning workshop to reduce Environmental Tobacco Smoking exposure. Laboratory Centre for Disease Control. Health Canada. Oct 1995.
23. Invited participant. Meeting to establish new priorities for funding. National Health Research and Development Programme of Canada. Montréal. Feb 1996.
24. Chair Scientific Advisory Committee for the Dalhousie University study of health effects of environmental and occupational pollution in the area of the Sydney, Nova Scotia steel industry. 1996.
25. Member of two Ministerial missions of the Quebec and Canadian governments to France to discuss with French experts the risks associated with low level exposure to chrysotile asbestos. Paris. Oct 1996.
26. Chair. Meeting of collaborators of European network of studies on lung cancer and smoking.
27. International Agency for Res. on Cancer, Lyon. June 1997.
28. Member of Canadian scientific delegation to United Kingdom to discuss with British experts the risk associated with low level exposure to chrysotile asbestos. London, Sept. 1997.
29. Symposium chair. Workshop to discuss methods of predicting numbers of cases of mesothelioma to be expected in various countries. Paris. Dec. 1997.
30. Invited participant and subgroup reporter. Peer Review on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by the Route of Inhalation. Health Canada and U.S. EPA. Ottawa. March 1998.
31. Co-chair. Workshop to explore the feasibility of an international collaborative study on use of cellular phones and risk of cancer. International Agency for Research on Cancer. Lyon. Feb 1999.
32. Panellist. Consensus Meeting for a Proposed Integrated National Health Surveillance Network. Health Canada. 1999.
33. Invited participant. Medical Research Council Summit Meeting on the new Canadian Institutes of Health Research. Toronto. June, 1999.
34. Invited participant. Planning group for an Institute of Population Health Research in CIHR. Jul-Dec 1999.
35. Invited speaker. Workshop for a Canadian Institute for Genetics Research. May 2000.
36. Invited participant. Workshop to explore the use of prospective cohorts to investigate gene-environment interactions in cancer etiology. National Cancer Institute. Rockville, MD. May 2000.
37. Invited participant. Founding meeting of Canadian Association for Workplace Safety and Health. Montréal. Jan 2001.
38. Invited participant. Workshop to advise Canadian Foundation for Innovation on its role in supporting population health research in Canada. Toronto, Feb 2001.
39. Invited participant. Consultative committee to advise Cancer Care Ontario on priorities in environmental cancer. April 2001.
40. Invited participant. Workshop on national priorities in cancer research. Institute for Cancer Research. CIHR. Toronto. May 2001.
41. Invited participant. Delphi process to advise Canadian Institutes of Health Research on priorities in cancer research. October-December 2001.
42. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
43. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.
44. Member of Advisory Panel. U.S. National Cancer Inst. Study of a Cohort of Chinese Workers Exposed to Benzene. 2002- .
45. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
46. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.

47. Organizer and Session Chair. International Epidemiological Association Meeting. Occupation and Health. Montréal. August, 2002.
48. Co-Organizer and Session Chair. Epidemiological Association Meeting. Asbestos and mesothelioma. Montréal. August, 2002.
49. Session Chair. Epidemiological Association Meeting. Environment and Health. Montréal Aug, 2002.
50. Invited participant. CIHR National Forum to devise a National Research Programme for Environmental Health. Ottawa. Sept 2002.
51. Invited participant. CIHR national forum on privacy of health data. Ottawa, November, 2002.
52. Member. Environmental and Occupational Carcinogens Advisory Group. Canadian Cancer Society. 2002 - 2004.
53. Participant. Meeting to discuss the establishment of a prospective childhood cohort in Canada. CIHR-IPPH. March 2004.
54. Member of working group on national cohort project. National Cancer Research Initiative. January-June 2004.
55. Member of advisory group on development of IDEES, Université de Montréal. January-June 2004.
56. Member, ad-hoc group to explore the feasibility of a Canadian cohort on cancer and chronic disease. 2004-2008.
57. Invited participant. Workshop to discuss the enhancement of population health research in Canada. CIHR-IPPH. June 2004.
58. Invited participant. Workshop on occupational cancer surveillance. Occupational Cancer Research & Surveillance Project (Cancer Care Ontario and the Ontario Workplace Safety & Insurance Board). February 2005.
59. Invited participant. Workshop on long-term large-scale cohorts. CIHR, December 2005.
60. Member. Advisory Scientific Committee. IBM – University of Alabama project on health of IBM manufacturing plant workers. 2006 - 2008.
61. Advisor and meeting participant. Ontario Workplace Safety and Insurance Board. Recommendations on how to develop occupational cancer research in Ontario. Toronto, 2005.
62. Invited participant. Workshop to estimate the burden of occupational cancer in the United Kingdom. UK Health and Safety Executive. Manchester. June 2006.
63. Advisory Committee to British Energy Networks Association. Workshop on the Future Needs of Electromagnetic Fields Occupational Studies in the Electric Utility Industry. Edinburgh. September 2006.
64. Advisory Committee. IARC Monograph Programme Planning of Special Volume 100. Lyon. September 2006.
65. Grant Review Panel. IVRSP. Paris. September 2006.
66. Advisory Committee to CCRA and ICR (CIHR) on the nature of a national cohort platform. Toronto, September 2006.
67. Invited participant. Comité d'éthique de la recherche de la faculté de médecine (CERFM) : Discussion d'un projet soumis pour la création d'une banque de données et de matériaux biologiques (Research Ethics Committee of the Faculty of Medicine: Review of a submitted project to create a bank of data and biologic samples). Université de Montréal. March 2007.
68. Invited participant. Workshop to Design and Implement the Ontario Cohort Consortium Research Platform. Toronto. June 2007.
69. Invited participant. Canadian Cancer Research Agencies. Strategic Planning Consultation in Montréal. May 2009.
70. Invited participant. IARC-NORA workshop to identify gaps of knowledge on occupational carcinogens, Lyon. June 2009.
71. Consultant. State of the science workshop: evaluation of epidemiological data consistency for application in regulatory risk assessment. US EPA and Johns Hopkins School of Public Health. Baltimore. September 2010.
72. Consultant. World Health Organisation. Re-evaluation of Risk Assessments related to DDT exposure. Geneva. November 2010.

73. Invited participant. WHO workshop to develop international guidelines for control of environmental carcinogens. Asturias. March 2011.
74. Session Chair. Discovering occupational carcinogens. Congress of Epidemiology. Montréal June 2011.
75. Invited co-organiser. Symposium of Environment and Cancer. Canadian Cancer Research Conference. Toronto. November 2011.
76. Invited organiser and Chair. Symposium on Cellphones and Cancer. American Association for Cancer Research. Chicago, April 2012.
77. Member Scientific Program Committee for the 2013 Canadian Cancer Research Conference, Toronto. November 2013.
78. Member of Advisory Committee to National Cancer Institute (U.S.) study on carcinogenicity of diesel emissions. 2017.

HONOURS

1. Biographee in various Who's Who in America versions. Since 1982
2. Perron-Desrosiers Prize. Granted by the Governing Council of the Institut Armand-Frappier. 1985.
3. Invited to give the annual Elizabeth Stern Memorial Lecture in U.C.L.A. School of Public Health. 1985.
4. National Health Scholar. National Health Research and Development Programme of Canada. 1988-1998.
5. Visiting Scientist Award. International Agency for Research on Cancer, Lyon. 1996-97.
6. Prix d'excellence. Institut national de la recherche scientifique. Université du Québec. 1999.
7. Distinguished Scientist Award. Medical Research Council, Canada. 1999-2004.
8. Canada Research Chair in Environmental Epidemiology and Population Health. 2001-2015.
9. Distinguished Scientist Lecturer. US National Cancer Institute. Division of Cancer Epidemiology and Genetics. 2006.
10. Cancer Research Society-Guzzo Chair in Environment and Cancer. Since 2007.
11. Fellow Canadian Academy of Health Sciences. Since 2008.
12. Geoffrey R Howe Distinguished Contributions Award, Canadian Society for Epidemiology & Biostatistics. 2011.
13. Ranked top Canadian public health researcher in terms of research productivity by Jarvey et al. 2012.

GRANT REVIEW, JOURNAL REVIEW AND PERSONNEL REVIEW

Associate Editor

American Journal of Epidemiology (1989-1998)

International Journal of Environmental Health (1991-)

Contributing Editor

Journal of Public Health Policy (1982-87)

American Journal of Industrial Medicine (1996-)

The Open Epidemiology Journal (2007-)

Chairman of grant review panels

National Health Research and Development Programme. Canada. (1990-94)

National Cancer Institute of Canada (1994-1995)

Member of grant review panels

40 times

External referee for tenure or promotion of personnel in other institutions

15 times

THESES

1. Siemiatycki J. "Space-time clustering: finding the distribution of a correlation-type statistic". M.Sc. thesis, McGill University, 1971.
2. Siemiatycki J. "Evaluation of strategies for household health surveys". Ph.D. thesis, McGill University, 1976.

ARTICLES PUBLISHED PEER REVIEW

1. Thurlbeck WM, Horowitz I, Siemiatycki J, Dunnill MS, Maisel JC, Pratt P, et al. Intra- and inter-observer variations in the assessment of emphysema. *Archives of Environmental Health*. 1969;18:646-59.
2. Becklake MR, Fournier-Massey G, McDonald JC, Siemiatycki J, Rossiter CE. Lung function in relation to chest radiographic changes in Quebec asbestos workers. *Bulletin de Physio-Pathologie Respiratoire*. 1970;6:637-59.
3. McDonald JC, McDonald AD, Gibbs GW, Siemiatycki J, Rossiter CE. Mortality in the chrysotile asbestos mines and mills of Quebec. *Archives of Environmental Health*. 1971;22:677-86.
4. Siemiatycki J, McDonald AD. Neural tube defects in Quebec: a search for evidence of 'clustering' in time and place. *British Journal of Preventive and Social Medicine*. 1972;26:10-4.
5. Siemiatycki J. Mantel's space-time clustering statistic: computing higher moments and a comparison of various data transforms. *Journal of Statistical Computation & Simulation*. 1978;7:13-31.
6. Siemiatycki J. A comparison of mail, telephone, and home interview strategies for household health surveys. *American Journal of Public Health*. 1979;69(3):238-45.
7. Siemiatycki J, Brubaker G, Geser A. Space-time clustering of Burkitt's lymphoma in east Africa: analysis of recent data and a new look at old data. *International Journal of Cancer*. 1980;25:197-203.
8. Siemiatycki J, Richardson L. Statut socio-économique et utilisation des services de santé à Montréal. *L'Actualité Economique*. 1980(Avril-Juin):194-210.
9. Siemiatycki J, Richardson L, Pless IB. Equality in medical care under national health insurance in Montréal. *New England Journal of Medicine*. 1980;303:10-5.
10. Colle E, Siemiatycki J, West R, Belmonte MM, Crepeau MP, Poirier R, et al. Incidence of juvenile onset diabetes in Montréal - demonstration of ethnic differences and socio-economic class differences. *Journal of Chronic Diseases*. 1981;34(12):611-6.
11. Siemiatycki J, Day NE, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. *Journal of the National Cancer Institute*. 1981;66(2):217-25.
12. Siemiatycki J, Thomas DC. Biological models and statistical interactions: an example from multistage carcinogenesis. *International Journal of Epidemiology*. 1981;10(4):383-7.
13. Siemiatycki JA, Richardson LJ. Le défi prioritaire en santé communautaire : Élargir notre vision pour atteindre nos véritables objectifs. *L'Union Médicale du Canada*. 1981;110:1008-12.
14. Pampalon R, Siemiatycki J, Blanchet M. Pollution environnementale par l'amiante et santé publique au Québec [Environmental asbestos pollution and public health in Quebec]. *L'Union Médicale du Canada*. 1982;111(5):475-82, 87-89.
15. Siemiatycki J, Gérin M, Richardson L, Hubert J, Kemper H. Preliminary report of an exposure-based, case-control monitoring system for discovering occupational carcinogens. *Teratogenesis, Carcinogenesis, and Mutagenesis*. 1982;2:169-77.
16. *Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. *American Journal of Epidemiology*. 1983;118(4):583-91.
17. Hours M, Fabry J, Siemiatycki J, Francois R. Diabète insulino-dépendant juvénile. Étude descriptive dans le département du Rhône. *Revue d'épidémiologie et de santé publique*. 1984;32:107-12.
18. Siemiatycki J, Campbell S. Nonresponse bias and early versus all responders in mail and telephone surveys. *American Journal of Epidemiology*. 1984;120(2):291-301.

19. Siemiatycki J, Campbell S, Richardson L, Aubert D. Quality of response in different population groups in mail and telephone surveys. *American Journal of Epidemiology*. 1984;120(2):302-14.
20. *Dewar RAD, Siemiatycki J. A program for point and interval calculation of odds ratios and attributable risks from unmatched case-control data. *International Journal of Bio-Medical Computing*. 1985;16:183-90.
21. Gérin M, Siemiatycki J, Kemper H, Bégin D. Obtaining occupational exposure histories in epidemiologic case-control studies. *Journal of Occupational Medicine*. 1985;27(6):420-6.
22. Siemiatycki J. Long-term funding for epidemiologic research. *Journal of Chronic Diseases*. 1985;38(3):211-2.
23. Thomas DC, Siemiatycki J, Dewar R, Robins J, Goldberg M, Armstrong BG. The problem of multiple inference in studies designed to generate hypotheses. *American Journal of Epidemiology*. 1985;122(6):1080-95.
24. Gérin M, Siemiatycki J, Bégin D, Kemper H, Lakhani R, Nadon L, et al. Dépistage épidémiologique des facteurs cancérigènes de l'environnement de travail montréalais: un premier bilan. *Travail et Santé*. 1986;2(3):S42-S6.
25. *Goldberg MS, Siemiatycki J, Gérin M. Inter-rater agreement in assessing occupational exposure in a case-control study. *British Journal of Industrial Medicine*. 1986;43:667-76.
26. Siemiatycki J, Colle E, Aubert D, Campbell S, Belmonte MM. The distribution of type I (insulin-dependent) diabetes mellitus by age, sex, secular trend, seasonality, time clusters, and space-time clusters: evidence from Montréal, 1971-1983. *American Journal of Epidemiology*. 1986;124(4):545-60.
27. Siemiatycki J, Richardson L, Gérin M, Goldberg M, Dewar R, Déry M, et al. Associations between several sites of cancer and nine organic dusts: results from an hypothesis-generating case-control study in Montréal, 1979-1983. *American Journal of Epidemiology*. 1986;123(2):235-49.
28. Thomas DC, Goldberg M, Dewar R, Siemiatycki J. Statistical methods for relating several exposure factors to several diseases in case-heterogeneity studies. *Statistics in Medicine*. 1986;5:49-60.
29. *Guay D, Siemiatycki J. Historic cohort study in Montréal's fur industry. *American Journal of Industrial Medicine*. 1987;12:181-93.
30. Siemiatycki J, Dewar R, Nadon L, Gérin M, Richardson L, Wacholder S. Associations between several sites of cancer and twelve petroleum-derived liquids. Results from a case-referent study in Montréal. *Scandinavian Journal of Work, Environment and Health*. 1987;13:493-504.
31. Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. Discovering carcinogens in the occupational environment: methods of data collection and analysis of a large case-referent monitoring system. *Scandinavian Journal of Work, Environment and Health*. 1987;13:486-92.
32. Diabetes Epidemiology Research International Group. Geographic patterns of childhood insulin-dependent diabetes mellitus. *Diabetes*. 1988;37:1113-9.
33. Siemiatycki J. Epidemiologic approaches to evaluation of carcinogens. In: *Living in a Chemical World*. Annals of the New York Academy of Sciences. 1988;534:395-9.
34. Siemiatycki J, Colle E, Campbell S, Dewar R, Aubert D, Belmonte MM. Incidence of IDDM in Montréal by ethnic group and by social class and comparisons with ethnic groups living elsewhere. *Diabetes*. 1988;37(8):1096-102.
35. Siemiatycki J, Gérin M, Stewart P, Nadon L, Dewar R, Richardson L. Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montréal. *Scandinavian Journal of Work, Environment and Health*. 1988;14:79-90.
36. Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. *Journal of Occupational Medicine*. 1988;30(8):617-25.
37. Siemiatycki J, Wacholder S, Dewar R, Wald L, Bégin D, Richardson L, et al. Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? *American Journal of Industrial Medicine*. 1988;13:59-69.

38. Gérin M, Siemiatycki J, Nadon L, Dewar R, Krewski D. Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montréal. *International Journal of Cancer*. 1989;44:53-8.
39. Siemiatycki J. Friendly control bias. *Journal of Clinical Epidemiology*. 1989;42(7):687-8.
40. Siemiatycki J, Colle E, Campbell S, Dewar RAD, Belmonte MM. Case-control study of IDDM. *Diabetes Care*. 1989;12(3):209-16.
41. Siemiatycki J, Dewar R, Lakhani R, Nadon L, Richardson L, Gerin M. Cancer risks associated with 10 inorganic dusts: results from a case-control study in Montréal. *American Journal of Industrial Medicine*. 1989;16(5):547-67.
42. Siemiatycki J, Dewar R, Richardson L. Costs and statistical power associated with five methods of collecting occupation exposure information for population-based case-control studies. *American Journal of Epidemiology*. 1989;130(6):1236-46.
43. Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. *Diabetes*. 1990;39:858-64.
44. Hours M, Siemiatycki J, Fabry J, Francois R. [Time clustering and temporospatial regrouping study of cases of juvenile diabetes in the district of Rhône (1960-1980)]. *Revue d'épidémiologie et de santé publique*. 1990;38(4):287-95.
45. Terracini B, Siemiatycki J, Richardson L. Cancer incidence and risk factors among Montréal residents of Italian origin. *International Journal of Epidemiology*. 1990;19(3):491-7.
46. *Dewar R, Siemiatycki J, Gérin M. Loss of statistical power associated with the use of a job-exposure matrix in occupational case-control studies. *Applied Occupational & Environmental Hygiene*. 1991;6:508-15.
47. Gérin M, Siemiatycki J. The occupational questionnaire in retrospective epidemiologic studies: recent approaches in community-based studies. *Applied Occupational & Environmental Hygiene*. 1991;6(6):495-501.
48. Payment P, Franco E, Richardson L, Siemiatycki J. Gastrointestinal health effects associated with the consumption of drinking water produced by point-of-use domestic reverse-osmosis filtration units. *Applied and Environmental Microbiology*. 1991;57(4):945-8.
49. Payment P, Richardson L, Siemiatycki J, Dewar R, Edwardes M, Franco E. A randomized trial to evaluate the risk of gastrointestinal disease due to consumption of drinking water meeting current microbiological standards. *American Journal of Public Health*. 1991;81(6):703-8.
50. Bégin D, Gérin M, de Guire L, Siemiatycki J, Adib G. Étude sur la validité des matrices emploi-exposition multisectorielles en hygiène industrielle. *Revue de médecine du travail*. 1992;XIX:74-9.
51. Soskolne CL, Jhangri GS, Siemiatycki J, Lakhani R, Dewar R, Burch JD, et al. Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. *Scandinavian Journal of Work, Environment and Health*. 1992;18(4):225-32.
52. Ursin G, Aragaki CC, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Oral contraceptives and premenopausal bilateral breast cancer: a case-control study. *Epidemiology*. 1992;3(5):414-9.
53. Payment P, Franco E, Siemiatycki J. Absence of relationship between health effects due to tap water consumption and drinking water quality parameters. *Water Science & Technology*. 1993;27(3/4):137-43.
54. Siemiatycki J. Problems and priorities in epidemiologic research on human health effects related to wiring code and electric and magnetic fields. *Environmental Health Perspectives*. 1993;101(Suppl. 4):135-41.
55. Case BW, Dufresne A, Fraser R, Siemiatycki J, Perrault G, Takahashi K. Decoding occupational history from total lung particulate analysis: Concordance between physico-chemical analysis and occupational histories. *Annals of Occupational Hygiene*. 1994;38(Supplement 1):469-82.
56. Korner-Bitensky N, Wood-Dauphinee S, Siemiatycki J, Shapiro S, Becker R. Health-related information postdischarge: telephone versus face-to-face interviewing. *Archives of Physical Medicine and Rehabilitation*. 1994;75(12):1287-96.

57. Siemiatycki J, Dewar R, Krewski D, Desy M, Richardson L, Franco E. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? *Epidemiology*. 1994;5(1):57-65.
58. Siemiatycki J, Dewar R, Nadon L, Gérin M. Occupational risk factors for bladder cancer: results from a case-control study in Montréal, Quebec, Canada. *American Journal of Epidemiology*. 1994;140(12):1061-80.
59. Takahashi K, Case BW, Dufresne A, Fraser R, Higashi T, Siemiatycki J. Relation between lung asbestos fibre burden and exposure indices based on job history. *Occupational & Environmental Medicine*. 1994;51(7):461-9.
60. Case BW, Dufresne A, Richardson L, Siemiatycki J, Takahashi K. Lung-retained dose following occupational exposure to silica. *Applied Occupational & Environmental Hygiene*. 1995;10(12):1031-6.
61. Nadon L, Siemiatycki J, Dewar R, Krewski D, Gerin M. Cancer risk due to occupational exposure to polycyclic aromatic hydrocarbons. *American Journal of Industrial Medicine*. 1995;28(3):303-24.
62. Siemiatycki J. Future etiologic research in occupational cancer. *Environmental Health Perspectives*. 1995;103 (Suppl 8):209-15.
63. Siemiatycki J, Krewski D, Franco E, Kaiserman M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *International Journal of Epidemiology*. 1995;24(3):504-14.
64. Upfal M, Divine G, Siemiatycki J. Design issues in studies of radon and lung cancer: implications of the joint effect of smoking and radon. *Environmental Health Perspectives*. 1995;103(1):58-63.
65. Ursin G, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Early adult body weight, body mass index, and premenopausal bilateral breast cancer: data from a case-control study. *Breast Cancer Research and Treatment*. 1995;33(1):75-82.
66. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational risk factors for prostate cancer: results from a case-control study in Montréal, Quebec, Canada. *American Journal of Epidemiology*. 1996;143(4):363-73.
67. *Fritschi L, Siemiatycki J. Melanoma and occupation: results of a case-control study. *Occupational & Environmental Medicine*. 1996;53(3):168-73.
68. *Fritschi L, Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. *International Journal of Cancer*. 1996;67(4):498-503.
69. *Fritschi L, Siemiatycki J, Richardson L. Self-assessed versus expert-assessed occupational exposures. *American Journal of Epidemiology*. 1996;144(5):521-7.
70. Haile RW, Witte JS, Ursin G, Siemiatycki J, Bertolli J, Thompson WD, et al. A case-control study of reproductive variables, alcohol, and smoking in premenopausal bilateral breast cancer. *Breast Cancer Research and Treatment*. 1996;37(1):49-56.
71. *Parent ME, Siemiatycki J, Renaud G. Case-control study of exposure to carbon black in the occupational setting and risk of lung cancer. *American Journal of Industrial Medicine*. 1996;30(3):285-92.
72. Siemiatycki J. Exposure assessment in community-based studies of occupational cancer. *Occupational Hygiene*. 1996;3:41-58.
73. *Parent ME, Siemiatycki J, Menzies R, *Fritschi L, Colle E. Bacille Calmette-Guerin vaccination and incidence of IDDM in Montréal, Canada. *Diabetes Care*. 1997;20(5):767-72.
74. Payment P, Siemiatycki J, Richardson L, Renaud G, Franco E, Prévost M. A prospective epidemiological study of gastrointestinal health effects due to the consumption of drinking water. *International Journal of Environmental Health Research*. 1997;7:5-31.
75. Siemiatycki J, *Fritschi L, Nadon L, Gerin M. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *American Journal of Industrial Medicine*. 1997;31(3):280-6.
76. Witte JS, Ursin G, Siemiatycki J, Thompson WD, Paganinihill A, Haile RW. Diet and premenopausal bilateral breast cancer - a case-control study. *Breast Cancer Research and Treatment*. 1997;42(3):243-51.

77. Boffetta P, Burdorf A, Goldberg M, Merler E, Siemiatycki J. Towards the coordination of European research on the carcinogenic effects of asbestos. *Scandinavian Journal of Work, Environment and Health*. 1998;24(4):312-7.
78. *Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *New England Journal of Medicine*. 1998;338(22):1565-71.
79. Gerin M, Siemiatycki J, Desy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene - results of a case-control study in Montréal. *American Journal of Industrial Medicine*. 1998;34(2):144-56.
80. Hu SW, Hertz-Picciotto I, Siemiatycki J. When to be skeptical of negative studies: pitfalls in evaluating occupational risks using population-based case-control studies. *Canadian Journal of Public Health Revue Canadienne de Sante Publique*. 1998;90(2):138-42.
81. *Parent ME, Siemiatycki J, Fritschi L. Occupational exposures and gastric cancer. *Epidemiology*. 1998;9(1):48-55.
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* First author was under supervision of J. Siemiatycki when this work was carried out.

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1. Siemiatycki J. Monitoring the occupational environment for carcinogens: a pilot study in Montréal. Working Environment and Health Seminar, McGill University, Department of Epidemiology, September 1978.
2. Siemiatycki J, Richardson L. Le défi prioritaire en santé communautaire: la protection et l'amélioration de l'environnement. Association pour la santé publique du Québec, Montréal, Quebec, October 1979.
3. Siemiatycki J. Occupational carcinogenesis. Séminaire départemental, Direction générale de la protection de la santé, Santé et Bien-être Social Canada, Ottawa, January 1981.
4. Siemiatycki J. An overview of problems in identifying occupational carcinogens. Canadian Labour Congress Meeting on Occupational Cancer, Montréal, February 1981.
5. Siemiatycki J. Feasibility of an exposure-based case-control approach to discovering occupational carcinogens: preliminary findings. Cold Springs Harbor Conference on Quantification of Occupational Cancer, Cold Springs Harbor, New York, March 1981.
6. Siemiatycki J. Dépistage des facteurs cancérigènes dans les milieux professionnels montréalais. Séminaire départemental, Département de médecine du travail et d'hygiène du milieu, Université de Montréal, Montréal, Quebec, March 1981.
7. Siemiatycki J. Surveillance program for occupationally related cancer. Société de Toxicologie du Canada, Montréal, Quebec, December 1981.
8. Gérin, J, Siemiatycki J. Translating job histories into histories of occupational exposure in an interview-based case-control Study. Medical Research Council Symposium on Job-Exposure Matrices, Southampton, England, April 1982.
9. Siemiatycki J. Rapporteur's report. Medical Research Council Symposium on Job-Exposure Matrices, Southampton, England, April 1982.
10. Siemiatycki J. Mortality in the general population in Quebec's asbestos mining areas. World Symposium on Asbestos, Montréal, May 1982.

11. Siemiatycki J. Occupational cancer epidemiology. McGill Department of Epidemiology seminar series, Montréal, Quebec, October 1982.
12. Siemiatycki J. Rapport d'une étude pilote qui vise à découvrir des agents cancérigènes de l'environnement professionnel. Institut Armand-Frappier, Laval, Quebec, October 1982.
13. Siemiatycki J, Richardson L, Gérin M. Discovering occupational carcinogens by an exposure-based case-control approach: feasibility and pilot study results. American Public Health Association Meeting, Montréal, Quebec, November 1982.
14. Siemiatycki J. Discovering occupational carcinogens by means of a novel exposure-based case-control approach. U.S. National Institute of Occupational Safety and Health seminar series. Cincinnati. November 1982.
15. Siemiatycki J. Dépistage des facteurs cancérigènes dans le milieu professionnel montréalais - rapport d'une étude pilote. Conférence-midi de l'Institut de recherche en santé et sécurité au travail, Montréal, Quebec, December 1982.
16. Siemiatycki J. Rapport d'une étude qui vise à découvrir des agents cancérigènes dans l'environnement professionnel. Conférence départementale, Université de Sherbrooke, Sherbrooke, Quebec, February 1983.
17. Siemiatycki J. Contribution of epidemiology to discovery of occupational carcinogens: case-control study in the Montréal area. Seminar Series, Lady Davis Institute, Jewish General Hospital, Montréal, March 1983.
18. Siemiatycki J. Hospital-based studies of environmental causes of cancer. Seminar series, McGill Cancer Centre and Montréal General Hospital, March 1983.
19. Siemiatycki J. Analyse préliminaire d'une enquête cas-témoins sur les expositions professionnelles et le cancer, INRS-Santé, Paris, France, April 1983.
20. Siemiatycki J. Découvrir les cancérigènes professionnels par des méthodes épidémiologiques. Congrès de l'ACFAS, Trois-Rivières, Quebec, May 1983.
21. Siemiatycki J. Surveillance of occupational cancer. University of Ottawa Special Course in Environmental Epidemiology, Ottawa, October 1983.
22. Gérin M, Richardson L, Siemiatycki J. Obtaining job exposure histories based on interview and expert assessment. Job Exposure Assessment Meeting. International Agency for Research on Cancer, Lyon, France, February 1984.
23. Siemiatycki J. Associations between bladder cancer and coffee and cigarette consumption: preliminary results of a case-control study. Environmental Risk Factors in Bladder Cancer Symposium, Lyon, February 1984.
24. Siemiatycki J. Preliminary results of an occupational cancer monitoring program. Kellogg Center Seminar Series. Montréal General Hospital, April 1984.
25. Siemiatycki J. Nickel, chromium and cancer: preliminary results from a case-control study. School of Occupational Health. McGill University, Montréal, April 1984.
26. Siemiatycki J. Les premiers résultats d'une stratégie épidémiologique visant à découvrir des produits cancérigènes dans l'environnement industriel. Micro-hebdo, Institut Armand-Frappier, May 1984.
27. Siemiatycki J. Cancer mortality in a general population highly exposed to asbestos. CAN-AM Chemical Congress. Montréal, June 1984.
28. Siemiatycki J. Some occupational and non-occupational risk factors for cancer: results from a multi-site case-control study in Montréal. Special seminar. Health Protection Branch of Health and Welfare Canada, January 1985.
29. Siemiatycki J. Premiers résultats d'un système de surveillance en épidémiologie visant à découvrir des agents cancérigènes dans le milieu industriel. Micro-Hebdo-Actualités, Institut Armand-Frappier, Laval, February 1985.
30. Siemiatycki J. Discovering environmental carcinogens. Elizabeth Stern Memorial Lecture. U.C.L.A. School of Public Health, Los Angeles, California, May 1985.
31. Siemiatycki J. Cancer surveillance. International Conference on Environmental and Occupational Significance of Industrial Carcinogens, Bologna, Italy, October 1985.

32. Siemiatycki J. Overview of an epidemiologic case-control approach to discovering occupational carcinogens. Special seminar. Health Department of Torino and Epidemiology Department of University of Torino, Torino, Italy, October 1985.
33. Siemiatycki J. Epidemiology of juvenile-onset diabetes in Montréal. Special lecture to Association of endocrinologists of Rhone-Alpes Region of France, Lyon, October 1985.
34. Siemiatycki J. Cancer risks associated with exposure to organic dusts. Special seminar. International Agency for Research on Cancer, Lyon, October 1985.
35. Siemiatycki J. Organic dusts and cancer. School of Occupational Health Seminar Series, McGill University, December 1985.
36. Gérin, M, Siemiatycki J, Richardson L, Begin, D, Kemper, H, Lakhani, R, Nadon L. Associations entre cancer et exposition professionnelle à diverses substances. Résultats d'une étude épidémiologique à Montréal. Association pour l'hygiène industrielle au Québec, VIII Congrès, City of Québec, Quebec, May 1986.
37. Siemiatycki J. Synthèse des résultats d'un système de surveillance épidémiologique des expositions professionnelles cancérigènes, Université Laval, May 1986.
38. Siemiatycki J. L'analyse des données appliquée à la santé et à la sécurité du travail. Symposium sur l'analyse de données, IRSST, Montréal, October 1986.
39. Siemiatycki J. An overview of epidemiologic contributions to the discovery of occupational carcinogens. Society of Toxicology of Canada, Montréal. December 1986.
40. Siemiatycki J, Wacholder, S, Dewar R, Begin, D, Richardson L, Rosenman, K, Gerin M. Smoking and degree of occupational exposure: are internal analyses likely to be confounded by smoking status? Symposium on Smoking in Occupational Cancer Studies. National Cancer Institute, Washington, December 1986.
41. Siemiatycki J. Petroleum-derived liquids and cancer risk: findings from a case-control study. McGill University, Department of Epidemiology, April 1987.
42. Siemiatycki J. Methods and findings from a case-control study of insulin-dependent diabetes mellitus in Montréal. Montréal Children's Hospital, May 1987.
43. Colle, E, Siemiatycki J. Epidemiologic and immunologic evidence concerning the etiology of insulin-dependent diabetes. Institut Armand-Frappier, May 1987.
44. Siemiatycki J. The role of epidemiology in environmental impact assessment. Symposium on Health in Environmental Impact Assessment. Canadian Public Health Association and Environment Canada, Ottawa, May 1987.
45. Siemiatycki J. Methods and results of a monitoring system for occupational carcinogens. Johns Hopkins University School of Public Health Seminar, Baltimore, Maryland, October 1987.
46. Siemiatycki J. Cancer risks associated with petroleum-derived liquids and combustion products. National Cancer Institute, Occupational Studies Section, Bethesda, Maryland, October 1987.
47. Gerin M, Siemiatycki J. Assessment of exposure to multiple agents in the workplace - experience from a population-based case-control study in Montréal. Workshop of European Economic Community on Methods of Assessment of Occupational Exposures for Epidemiologic Detection of Cancer Risks, Paris, February 1988.
48. Siemiatycki J. Overview of epidemiologic tasks. International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health. Toronto, March 1988.
49. Siemiatycki J. Results of an exposure-based case-control study of occupational carcinogens. Ontario Cancer Treatment and Research Foundation, Toronto, April 1988.
50. Siemiatycki J. Methodology of cancer case-control studies. Special Lecture Series in McGill Summer Program in Epidemiology, Montréal, May 1988.
51. Siemiatycki J. Costs and benefits of various approaches to estimating occupational cancer risks in case-control studies. Symposium on Occupational Cancer Epidemiology. Vancouver, June 1988.
52. Richardson L.R, Siemiatycki J, Dewar R. How well does a job exposure matrix reflect the exposure assessment of individually coded job histories? Workshop on job exposure matrices held at INSERM, Paris, October 1988.

53. Siemiatycki J. Methodologic issues in an exposure-based case-control study for discovering occupational carcinogens. Medical Research Council, Biostatistics Unit, Cambridge, England, December 1988.
54. Siemiatycki J. A synthesis of findings from an occupational cancer case-control study. Invited seminar in Department of Epidemiology, School of Public Health, University of North Carolina. Chapel Hill, North Carolina, April 1989.
55. Siemiatycki J. Methodologic problems in assessing exposure status for case-control studies. National Cancer Institute Seminar, Silver Spring, Maryland. April 1989.
56. Siemiatycki J. Environmental causes of cancer. McGill Cancer Center Public Lecture Series, Montréal. May 1989.
57. Siemiatycki J. Approches épidémiologiques dans l'investigation des facteurs cancérigènes. Summer course in community health, Université Laval, City of Québec, Quebec, June 1989.
58. Krewski, D, Siemiatycki J, Nadon L, Dewar R, Gerin M. Cancer risks due to occupational exposure to PAH's. International Conference on Genetic Toxicology of Complex Mixtures, Washington, District of Columbia, September 1989.
59. Siemiatycki J. Discovering environmental carcinogens by means of a case-control methodology. Dalhousie University, Faculty of Medicine seminar, December 1989.
60. Siemiatycki J. Using epidemiologic evidence in compensation of industrial disease. Special workshop of Industrial Disease Standards Panel of Ontario, Toronto, December 1989.
61. Siemiatycki J. Epidemiologic approaches to evaluating the carcinogenicity of complex mixtures. Workshop on carcinogenicity of Complex Mixtures. National Academy of Sciences of the U.S.A., Tucson, January 1990.
62. Siemiatycki J. Review of findings from a registry-like database designed to discover occupational carcinogens. Workshop on Indicators of Environmental Health. Waterloo Institute for Risk Research and Health and Welfare Canada, Ottawa, March 1990.
63. Siemiatycki J. Findings from an occupational cancer case-control study. Invited seminar in Department of Clinical Epidemiology, Royal Victoria Hospital. Montréal, March 1990.
64. Siemiatycki J. Effect of exposure strategies on risk estimates and statistical power. International Workshop on Retrospective Exposure Assessment for Occupational Epidemiologic Studies, Leesburg, Virginia, March 1990.
65. Siemiatycki J. Discovering environmental carcinogens: an epidemiologic perspective. Invited seminar in Department of Epidemiology, School of Public Health, University of North Carolina. Chapel Hill, North Carolina, March 1990.
66. Siemiatycki J. Discovering environmental carcinogens: review of an epidemiologic surveillance project. Invited seminar in Occupational & Environmental Health Unit, University of Toronto, Toronto, April 1990.
67. Siemiatycki J. Environnement et cancer: une perspective épidémiologique. 58th Association canadienne française pour l'avancement des sciences. Colloque santé et environnement, City of Québec, Quebec, April 1990.
68. Payment P, Richardson L, Edwards M, Franco E, Siemiatycki J. Drinking water related illness: an epidemiological study. Second International Biennial Water Quality Symposium: Microbiological Aspects, Vina Del Mar, Chile, August 1990.
69. Siemiatycki J. Occupational cancer. Seminar series of Laboratory Centre for Disease Control, Health and Welfare Canada, Ottawa, March 1991.
70. Siemiatycki J. A decade of searching for occupational carcinogens: methods and results of a case-control study. Seminar series of the Division of Clinical Epidemiology, Montréal General Hospital, Montréal, March 1991.
71. Siemiatycki J. Detecting occupational carcinogens using epidemiologic methods: results and their interpretation. McGill University, Department of Epidemiology and Biostatistics, Summer Lecture Series, Montréal, June 1991.
72. Siemiatycki J. Overview of results of an occupational cancer monitoring study. School of Public Health, University of California at Berkeley, Berkeley, October 1991.

73. Siemiatycki J. Discussant of paper on Mortality of oil refinery and distribution workers. International Symposium on the Health Effects of Gasoline, Miami, November 1991.
74. Begin, D, Gerin M, De Guire L, Siemiatycki J, Adib G, Fournier C. Étude sur la validité des matrices emploi-exposition multisectorielles en hygiène industrielle. Scientific Committee on Computing in Occupational and Environmental Health, III International Workshop, Paris, November 1991.
75. Siemiatycki J. Cancer et travail : connaissances actuelles, approches antérieures et nouvelles. Colloque de l'Association des médecins du travail du Québec, Montréal. June 1992.
76. Siemiatycki J. Risques de cancers reliés aux expositions chimiques en milieu de travail: résultats d'une étude épidémiologique à Montréal. IRSST, Montréal, November 1992.
77. Siemiatycki J. Carcinogens in the occupational environment. Invited seminar in School of Public Health, University of North Carolina, Chapel Hill, North Carolina. December 1992.
78. Siemiatycki J. Discussant of invited seminar on risk assessment. School of Occupation Health, McGill University, March 1993.
79. Siemiatycki J. Are the effects of smoking on lung and bladder cancer confounded by occupational carcinogens? Invited seminar given at the Michigan Cancer Foundation, Detroit and at the University of Michigan, Ann Arbor, May 1993.
80. Siemiatycki J. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? McGill University, Department of Epidemiology and Biostatistics, Montréal, December, 1993.
81. Siemiatycki J. Occupational causes of cancer. President's Cancer Panel Meeting on Avoidable Causes of Cancer, Bethesda, April 1994.
82. Siemiatycki J. Retrospective exposure assessment in community-based studies. Conference on Retrospective assessment of occupational exposures in epidemiology, IARC, Lyon, April 1994.
83. Siemiatycki J. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? Department of Human Oncology, University of Torino, Torino, Italy, April 1994.
84. Siemiatycki J. Risque de cancer dû au tabagisme. Département de médecine sociale et préventive, Université Laval, Québec, May 1994.
85. Siemiatycki J. Registry studies of bladder cancer. NCI Workshop on Occupational Exposures and Urogenital Cancers, Rockville, May 1994.
86. Siemiatycki J. Facteurs de risques environnementaux pour le cancer: une perspective épidémiologique. Atelier sur la recherche en cancer, Université du Québec à Rimouski, April 1995.
87. Camus M, Siemiatycki J. Non-occupational exposure to asbestos: how to assess dose and risk. McGill University, Department of Epidemiology and Biostatistics. Montréal, May 1995.
88. Siemiatycki J. Occupational carcinogens in Montréal. Seminar - International Agency for Research on Cancer, Lyon, France, June 1995.
89. Siemiatycki J. Occupational causes of cancer: findings from a large scale case-control study of occupational cancer. Department of Medical Informatics, Biometry and Epidemiology, University of Essen, Essen, Germany, July 1995.
90. Siemiatycki J. Assessing occupational exposures in community based epidemiological studies. Bremen Institute for Preventive and Social Medicine, Bremen, Germany, July 1995.
91. Case, B, Camus M, Richardson L, Siemiatycki J. Ascertainment of mesothelioma among Québec women from 1970 to 1990. Special Symposium on Mesothelioma, IRSST, Montréal, August 1995.
92. Siemiatycki, J. Une nouvelle approche épidémiologique pour le dépistage de cancérrogènes en milieu de travail. Club de recherches cliniques du Québec, Bromont, Quebec, September 1995.
93. Siemiatycki J. Occupational causes of cancer: findings from a large scale case-control study of occupational cancer. Special seminar. School of Public Health, Univ. of Michigan, Ann Arbor, Michigan, June 1996.
94. Siemiatycki J. An empirical evaluation of the magnitude of confounding bias. Statistical Society of Canada, Waterloo, June 1996.

95. Siemiatycki J. Occupational exposures and cancer risk: recent results and methodological insights from a population-based case-control study in Montréal. Department of Epidemiology & Biostatistics, McGill University. October, 1996.
96. Siemiatycki J. Utilités et limites des études épidémiologiques dans l'évaluation des risques environnementaux. ACFAS, City of Québec, Quebec, May 1998.
97. Siemiatycki J. International collaboration in cancer epidemiology. Society for Epidemiology Research, Chicago, June 1998.
98. Siemiatycki J. Accuracy of the EPA risk assessment model for predicting the risk of lung cancer at environmental levels of asbestos exposure. National Cancer Institute, Rockville, Maryland, March 1999.
99. Siemiatycki J. Risk of lung cancer at environmental levels of asbestos exposure. University of Toronto, Toronto, September 1999.
100. Siemiatycki J. Estimating risks due to low level exposures. Society for Epidemiology Research, Seattle, June 2000.
101. Siemiatycki J. Debater on the proposition that research is a top priority in occupational cancer prevention. Preventive Oncology Seminar, Cancer Care Ontario, Toronto, April 2001.
102. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. Various aspects of smoking behavior on lung cancer risk: a flexible modeling approach. National Cancer Institute, Bethesda, May 2001.
103. Siemiatycki J. Challenges to epidemiology and challenges to Canadian epidemiologists. National Student Conference of Epidemiology, Toronto, June, 2001.
104. Siemiatycki J. President's address. Congress of Epidemiology, Toronto, June, 2001.
105. Siemiatycki J. Découvrir les cancérigènes dans l'environnement: bilan des activités de recherche passées et perspectives d'avenir. Département de médecine sociale et préventive, Université de Montréal, October 2001.
106. Siemiatycki J. Risque de cancer chez les femmes résidentes des villes des mines d'amianté québécoises: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque (« risk assessment ») du E.P.A. Département de santé environnementale, Université de Montréal, October 2001.
107. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Relations dose-réponse entre la fumée de cigarette et le cancer pulmonaire à partir d'une étude cas-témoins à Montréal : Estimations utilisant une modélisation flexible. Congrès INRS-Institut Armand-Frappier, Sainte-Adèle, Quebec, November 2001.
108. Siemiatycki J, Camus M, Case B, Desy M, Parent, M.-É. Risque de cancer chez les résidentes des villes de l'amianté au Québec: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque de l'E.P.A. Symposium sur l'amianté of Institut national de santé publique du Québec, Montréal, December 2001.
109. Laplante O, Parent M.-É, Siemiatycki J. Risque de mésothéliome et de cancer du poumon associé à l'exposition professionnelle aux fibres d'amianté, Montréal 1979-85. Symposium de l'Institut national de santé publique du Québec, Montréal, December 2001.
110. Siemiatycki J. Occupational causes of cancer: overview of the contribution of a study in Montréal, Research Day at Dept of Epidemiology and Community Medicine, University of Ottawa, April 2002.
111. Siemiatycki J. Biostatistical problems in epidemiologic case-control studies. Statistical Society of Canada, Hamilton, Ontario, May 2002.
112. Leffondre K, Abrahamowicz M, Siemiatycki J. Definition of risk sets for Cox's analysis of case-control data with time-varying exposures: A simulation study. Intended Society for Clinical Biostatistics (ISCB), Dijon, France, September 2002.
113. Siemiatycki J. Occupational causes of cancer. CCERN and Health Canada Research Workshop, Montebello, Quebec. October 2002.
114. Siemiatycki J. Occupational causes of cancer. Departmental seminar, McGill University, Montréal. November 2002.
115. Siemiatycki J. Facteurs environnementaux dans l'étiologie du cancer. Retraite annuelle du centre de recherche du CHUM, St-Sauveur, Quebec. November 2002.
116. Siemiatycki J. Environmental and occupational causes of cancer. Seminar. Cancer Care Ontario, Toronto, February 2003.

117. Siemiatycki J. The state of epidemiology in Canada. Plenary address. CSEB Student Congress, Halifax, Nova Scotia, June 2003.
118. Siemiatycki J. Occupational cancer epidemiology: the evolving big picture. Distinguished Scientist Lecture, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville MD, October 2003.
119. Siemiatycki J. Challenges in cancer epidemiology. Meeting of the Institute Advisory Board of Institute for Cancer Research, CIHR, Montréal, June 2004.
120. Siemiatycki J. Keynote address. Occupation and cancer. International Association of Cancer Registries, Beijing, September 2004.
121. Siemiatycki J. Which cancers are most important, what are the associated occupational situations and which confounders are involved? Burden of Cancer Epidemiologic Workshops, Health and Safety Executive. Manchester, UK, November 2004.
122. Siemiatycki J. Occupational causes of cancer. New Strategies for Recognizing and Preventing Occupational Disease, Canadian Center for Occupational Health and Safety, Toronto, March 2005.
123. Siemiatycki J. Occupational causes of cancer. The Respiratory Epidemiology & Clinical Research Unit, Montréal Chest Institute, Montréal, March 2005.
124. Siemiatycki J. Environnement et cancer : quels sont les risques? Les Belles Soirées public lecture series, Université de Montréal, Montréal, April 2005.
125. Siemiatycki J. An overview of environmental, occupational & lifestyle causes of lung cancer. Cancer Axis, McGill University Hospital Centre Research Institute, Montréal, June 2005.
126. Siemiatycki J. Les règles des comités d'éthique vont amputer notre capacité de prévenir des maladies et sauver des vies. Réunion de FRSQ sur les banques de données et des matières biologiques, Montréal, June 2005.
127. Siemiatycki J. Introductory comments. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
128. Siemiatycki J. The burden of occupational cancer on workers and on society. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
129. Siemiatycki J. Revue des expositions professionnelles associées au cancer (Review of occupational exposures associated with cancer): pre-conference training session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
130. Siemiatycki J. Opening session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
131. Siemiatycki J. Impact de l'environnement et du milieu de travail sur le cancer : connaissances récentes. 9es Journées annuelles de santé publique (JASP), City of Québec, Quebec, November 2005.
132. Siemiatycki J. La recherche épidémiologique sur le cancer. Canadian Cancer Society - 2005 Annual Conference, City of Québec, Quebec, November 2005.
133. Siemiatycki J. Occupational EMF exposure and risk of cancer – methodological considerations. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry, Edinburgh, September 2006.
134. Siemiatycki J. What is known about the modifiable causes of cancer and why we will not learn much more: Reflections on the decline of epidemiology as a tool to elucidate disease etiology. Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montréal, October 2006.
135. Siemiatycki J. Keynote Speaker. Environmental causes of cancer. 28th Annual Meeting of the International Association of Cancer Registries, Goiania, Brazil, November 2006.
136. Parent M.-E, Rousseau M.-C, Siemiatycki J, Boffetta P, Cohen A. Using the workplace as a window to study the role of diesel and gasoline engine emissions in lung cancer development. Invited abstract submitted to the Eleventh International Congress of Toxicology, Montréal, Quebec, July 2007.
137. Siemiatycki J. Keynote Speaker. The future of occupational epidemiology? 19th International Conference on Epidemiology in Occupational Health (EPICOH 2007), Banff, October 2007. *Occup. Environ. Med.* 2007 Dec; 64:46.

138. Siemiatycki J. Relationship between environmental risks and health of seniors. Workshop on Seniors' Health and the environment. Health Canada, Ottawa, February 2008.
139. Siemiatycki J. Freedom of research - is it threatening or threatened? Conference of Institutional Review Boards of Quebec, (4e Journées d'étude des CER), City of Québec, Quebec, October 2008.
140. Siemiatycki J. Cancer and Environment – Annual University of Montréal Medical Faculty Assembly, Montréal, December 2008.
141. Siemiatycki J. Impact de l'environnement et du milieu de travail sur les risques de cancer : méthodologie de recherche et résultats. Conférence en santé publique, Université Laval, May 2009.
142. Siemiatycki J. CIHR and Epidemiologic Research. CSEB, Ottawa, May 2009.
143. Siemiatycki J. Mode de vie, milieu de vie: les causes modifiables du cancer. (Lifestyles and environment: modifiable causes of cancer). Keynote address. Conference nationale pour vaincre le cancer, Montréal April 2010.
144. Siemiatycki J. Montréal case-control studies on occupation and cancer. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
145. Siemiatycki J. Modifiable causes of cancer and estimates of attributable fractions. Presentation for II International Course on occupational cancer, Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
146. Siemiatycki J. Asbestos and cancer in Quebec: a presentation of studies in three populations. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
147. Siemiatycki J. An overview of recognized environmental and lifestyle causes of cancer, and their contribution to the overall burden of cancer. International Congress of Pathophysiology, Montréal, September 2010.
148. Siemiatycki J. Les causes modifiables du cancer (Lifestyles and environment: modifiable causes of cancer). Conference annuelle de la Société du cancer du Canada, division Québec, November 2010.
149. Siemiatycki J. Alison McDonald's research on the impact of Medicare in Québec. Department of Epidemiology and Biostatistics, McGill University, Montréal, Quebec, May 2011.
150. Siemiatycki J. An overview of environmental causes of cancer. Special Symposium to honour Nobel Prize winner CRCHUM, Montréal, Quebec, June 2011.
151. Siemiatycki J. Review of IARC evaluation on cellphones and cancer. Congress of Epidemiology, Montréal, Quebec, June 2011.
152. Siemiatycki J. L'évidence concernant les risques de cancer liés à l'utilisation du téléphone cellulaire. Institut national de santé publique du Québec, October 2011.
153. Siemiatycki J. Do cellphones cause brain cancer? Canadian Cancer Research Conference, Toronto, November 2011.
154. Siemiatycki J. Do cellphones cause brain cancer? Canadian Center for Architecture. Public science lecture series, Montréal, Quebec, January 2012.
155. Siemiatycki J. Do cellphones cause brain cancer? McGill University Department of Epidemiology lecture series, Montréal, Quebec, March 2012.
156. Siemiatycki J. L'environnement et le risque de cancer. Table ronde. Conference annuelle de la Coalition Cancer, Montréal, Quebec, March 2012.
157. Siemiatycki J. An Overview of Modifiable Risk Factors for Cancer. CHUM Department of Medicine, Montréal, Quebec, March 2012.
158. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Grand Rounds, St-Mary's Hospital, Montréal, Quebec, September 2012.
159. Siemiatycki J. The epidemiology of cell phones and brain cancer. Centre hospitalier universitaire Vaudois, Lausanne, Suisse, October 2012
160. Siemiatycki J. Occupational causes of cancer. Annual meeting of Occupational & Environmental Medical Association of Canada, Montréal, Quebec, September 2013.
161. Siemiatycki J. Fraction of lung cancer that is legally attributable to smoking: a novel parameter. ISPED, Bordeaux, France, November 2013.

162. Siemiatycki J. Some challenges in environmental cancer research. Boston University School of Public Health, Boston, Massachusetts, February 2014.
163. Siemiatycki J. Les causes modifiables du cancer: le cancer peut être évité. Symposium de La Fondation Sauve Ta Peau, Montréal, Quebec, September 2014.
164. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. BIPS, Bremen, Germany, September 2015.
165. Siemiatycki J. Insights into the use of epidemiologic data in a class action lawsuit against the tobacco industry. CRCHUM division seminar, Montréal, Quebec, September 2015.
166. Siemiatycki J. Development of a methodology to estimate legally attributable fraction of lung cancer attributable to cigarette smoking. McGill Univ Dept of Epidemiology, Montréal, Quebec, October 2015.
167. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. SIRIC-BRIO Cancer Centre. Bordeaux, France, November 2015.
168. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Dept of Medicine, CHUM, Montréal, Québec, November 2015.
169. Siemiatycki J. Occupation and cancer. Conference for the 50th Anniversary of IARC, Lyon, June 2016.
170. Siemiatycki J. Contribution of epidemiology to knowledge on occupational risk factors for cancer. 34e Congrès national de Médecine et Santé au Travail, Paris, France, June 2016.
171. Siemiatycki J. The influence of JC McDonald on the evolution of epidemiology in Canada. Symposium in honour of JC McDonald. McGill Univ., Montréal, Quebec, May 2017.
172. Siemiatycki J. A survey of knowledge on occupational causes of cancer. Keynote address. International Association of Cancer Registries, Utrecht, Netherlands, October 2017.
173. Siemiatycki J. La preuve statistique au tribunal : recours collectif en situation d'incertitude. Café-statistique de la Société des statisticiens français de la région parisienne, Paris, France, May 2018.

SCIENTIFIC PRESENTATIONS - OFFERED AND ACCEPTED

1. Siemiatycki J. Comparison of mail, telephone and home interview methods for health surveys. International Epidemiologic Association Meeting. Puerto Rico. August 1977.
2. Siemiatycki J, Day NE, Fabry J, Cooper, JA. Identification d'agents cancérigènes dans le milieu de travail: un nouveau système épidémiologique de monitoring. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
3. Siemiatycki J, Richardson L, Pless B. Equality in Medical Care under National Health Insurance in Montréal. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
4. Siemiatycki J. Discovering occupational carcinogens. International Symposium on Chemical Mutagenesis, Human Population Monitoring and Genetic Risk Assessment. Ottawa. October 1980.
5. Siemiatycki J, Richardson L, Gerin M. Discovering occupational carcinogens by a substance-based case-control approach-fieldwork considerations. International Epidemiologic Association Meeting. Edinburgh. August 1981.
6. Siemiatycki J, Colle E, West R, Belmonte M. Space-time clustering of juvenile-onset diabetes in Montréal. International Epidemiologic Association Meeting. Edinburgh. August 1981.
7. Siemiatycki J, Gerin M, Richardson L. Discovering occupational carcinogens by an exposure-based case-control approach: exposure assessment aspects. Second International Symposium on Epidemiology in Occupational Health. Montréal, August 1982.
8. Siemiatycki J, Gerin M, Lakhani R, Dewar R, Pellerin J, Richardson L. Nickel and cancer associations from a multicancer occupation exposure case-referent study. Symposium on Nickel in the Environment. Lyon, March 1983.
9. Gerin M, Siemiatycki J. La traduction des histoires professionnelles en histoires d'expositions chimiques: un défi pour l'hygiéniste du travail. Congrès de l'Association pour l'hygiène industrielle du Québec. Quebec, May 1983.
10. Siemiatycki J, Colle E, Campbell S, Belmonte M. Preliminary analysis of a case-control study of Type I diabetes mellitus. Baltimore, June 1985.

11. Siemiatycki J, Richardson L, Gerin M, Goldberg M, Dewar R. Associations between nine sites of cancer and nine organic dusts: results from a hypothesis-generating case-control study in Montréal. Society for Epidemiologic Research. Chapel Hill, North Carolina, June 1985.
12. Richardson L, Siemiatycki J, Gerin M, Goldberg M, Dewar R, Desy M, Campbell S, Wacholder S. Associations between several sites of cancer and nine organic dusts: results from a case-control study. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
13. Richardson L, Siemiatycki J. Case-control study methods: when to interview subjects and non-response bias. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
14. Soskolne C, Jhangri G, Checkoway, Risch H, Siemiatycki J, et al. Sulphuric acid exposure in laryngeal cancer: induction and latency estimates from a lagged exposure window analysis. XII Scientific Meeting of the International Epidemiology Assoc. Los Angeles, August, 1990.
15. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1989). Gastrointestinal illness and drinking water: a prospective epidemiological study. 57th Conjoint Meeting on Infectious Diseases (CACMID), Montréal, 25-29 November 1989, Résumé C-30.
16. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). Drinking water related gastrointestinal illnesses. 1990 Annual Meeting of the American Society for Microbiology, Anaheim California, 13-17 May 1990.
17. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). A prospective epidemiological study of drinking water related gastrointestinal illnesses. International Association on water Pollution Research and Control, Health Related Water Microbiology Group, Tubingen, West Germany, 1-6 April 1990.
18. Case BA, Dufresne A, Siemiatycki J, Fraser R. Decoding occupational history from total lung particulate analysis. II: A comparative study. Brit. Occ. Hyg. Soc.; Seventh International Symposium on Inhaled Particles, Edinburgh, September 1991, S4.5.
19. Suarez-Almazor M, Soskolne C, Fung K, Jhangri G, Burch D, Howe G, Miller A, Siemiatycki J, Lakhani R, Dewar R. Choice of summary worklife exposure measures in the estimation of risk: an empirical assessment. Canadian Epidemiology Symposium. Edmonton. May. 1991.
20. Siemiatycki J, Nadon L, Dewar R. Cancer risks due to occupational exposure to polycyclic aromatic hydrocarbons. 8th International Symposium on Epidemiology in Occupational Health, Paris, France, September 1991.
21. Bourbonnais R, Siemiatycki J. Socioeconomic variables and cancer risk. Canadian Society for Epidemiology and Biostatistics. Edmonton, May 1991.
22. Gerin M, Begin D, Siemiatycki J, Dewar R. Study on the validity of the NOES job-exposure matrix using industrial hygiene measurements obtained in Montréal. Conference on Retrospective Assessment of Occupational Exposure. IARC Lyon. April 1994.
23. *Camus M, Siemiatycki J. Estimating past asbestos fiber levels in the general population of asbestos mining towns in Quebec. International Society Environmental Epidemiology, Research Triangle Park, N.C. Sept. 1994.
24. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. Canadian Society for Epidemiology and Biostatistics. St-John's, Newfoundland, Aug 1995.
25. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. International Society for Environmental Epidemiology. Noordwijkerhout, Netherlands, Aug, 1995.
26. Case BW, Camus M, Siemiatycki J. Trends in Pathologic Diagnosis of Malignant Mesothelioma among Quebec Women 1970-1990. Royal College of Medicine. Montréal. Sept. 1995.
27. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational Risk Factors for Prostate Cancer. Canadian Society for Epidemiology and Biostatistics, St-John's, Newfoundland, Aug 1995.
28. *Camus M, Siemiatycki J. The Estimation of Past Asbestos Fiber Levels in Quebec Asbestos Mining Towns from 1900 to 1984. Canadian Society for Epidemiology & Biostatistics, St-John's, Newfoundland, Aug 1995.

29. *Camus M, Siemiatycki J, Dewar R. Non-Occupational Asbestos Exposure and Risk of lung Cancer in the Female Population of Asbestos-Mining Towns: Implications for Risk Assessments. Canadian Society for Epidemiology and Biostatistics Meeting, St-John's, Newfoundland, Aug 1995.
30. Payment P, Franco E, Siemiatycki J, Richardson L, Renaud G, Prevost M. Epidemiology studies of tap-water related gastrointestinal illnesses. Water Quality Technology Conference, New Orleans, Nov. 1995.
31. *Fritschi L, Siemiatycki J. Self-assessed versus expert-assessed occupational exposures. Canadian Society for Epidemiology and Biostatistics Meeting, St Johns, Newfoundland, Aug 1995.
32. Payment P, Siemiatycki J, Richardson L, Renaud G. Épidémiologie des maladies gastro-intestinales et respiratoires: incidence, fraction attribuable à l'eau et coûts pour la société. ACFAS, Montréal, May 1996.
33. *Fritschi L, Parent M-É, Siemiatycki J. Gastric cancer and occupation. Australasian Epidemiological Association, Victoria, Australia. July 1996.
34. *Camus M, Case BW, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.1: Environmental exposure assessment. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
35. Case BW, Camus M, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.2: Mesothelioma: observed vs. predicted. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
36. *Camus M, Siemiatycki J. Cancer risks due to non-occupational asbestos exposure. Can. Soc. for Epidemiol. & Biostat. London, Ontario, May 1997.
37. Weston TL, Aronson KJ, Howe GR, Nadon L, Siemiatycki J. Cancer mortality risk in a cohort of working men. Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
38. *Parent M-É, Siemiatycki J, Menzies L, Fritschi L, Colle E. Can Bacille-Calmette Guérin vaccination prevent insulin-dependent diabetes mellitus (IDDM)? Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
39. Wolf, S, Siemiatycki J, Beyersmann, D, Jockel, K. H. A case-control study of lung cancer - performance of a job-exposure matrix for cadmium, chromium, nickel, and stainless steel dust. Internat. Epidemiol. Assoc. European Region Meeting. Munster, Germany, Sept. 1997.
40. *Parent, M.E. Siemiatycki J. Exposition professionnelle aux émissions d'essence et de diesel, et cancer du poumon. ACFAS, Quebec, May 1998.
41. *Parent M-É, Siemiatycki J, Boffetta P. Occupational exposure to gasoline and diesel engine emissions and lung cancer. Soc. Epid. Res, Chicago, June 1998.
42. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Occupational exposure to gasoline and diesel exhausts and lung cancer. Inter. Soc. Environ. Epid, Boston, August 1998.
43. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Gasoline and diesel engine emissions in the workplace and lung cancer. PREMUS-ISEOH '98, Helsinki, Finland, Sept. 1998.
44. Leffondre K, Abrahamowicz M, Rachet B, Siemiatycki J. Modeling smoking history: A comparison of different approaches. Congress of Epidemiology, Toronto, June 2001.
45. Fritschi L, Nadon L, Benke G, Lakhani R, Latreille B, Parent M-É, Siemiatycki J. Validation of expert assessment of occupational exposures X2001 – Occupational Exposure Assessment for Epidemiology and Practice, Gothenburg, Sweden, June 2001.
46. Parent M-É, Siemiatycki J, Desy M. Case-control study of occupational exposures and risk of prostate cancer among farmers. Case-control study of occupational exposures and risk of prostate cancer among farmers, Toronto, June 2001.
47. Siemiatycki J, Camus M, Parent M-É, Richardson L, Desy M, Case BW. Case-control study of pleural mesothelioma among women in Quebec chrysotile mining regions. Inhaled Particles IX (BOHS), Cambridge, United Kingdom, September 2001.
48. Jockel K-H, Wolf S, Ahrens W, Jahn I, Pohlabein H, Beyersmann D, Siemiatycki J. Cadmium as a human lung carcinogen. Jahrestagung der Deutschen Arbeitsgemeinschaft für Epidemiologie (DAE) [Annual convention of the German epidemiology working group], Garmisch-Partenkirchen, Germany, September 2001.

49. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Annual Meeting of the Statistical Society of Canada (SSC). Hamilton, Ontario. May 2002.
50. Parent M-É, Siemiatycki J, Desy M. Association between Alcohol Consumption and Each of 23 Types of Cancer in Men. Soc. Epid. Res, Palm Desert, California, June 2002.
51. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Society for Epidemiologic Research (SER), Palm Desert, California, June 2002.
52. Rachet B, Parent M-É, Siemiatycki J. Welding Fumes and Lung Cancer: A Case-Control Study, Soc. Epidemiol. Res, Palm Desert, California, June 2002.
53. Rachet B, Abrahamowicz M, Sasco A, Siemiatycki J. Flexible estimation of the distribution of lag in the effects of exposures and interventions. 34th Annual SER Meeting. Palm Desert, California. June 2002.
54. Abrahamowicz M, Mackenzie T, Leffondre K, Du Berger R, Siemiatycki J. Joint modeling of time-dependent and non-linear effects of continuous predictors in survival analysis, with application to reassess the impact of intensity of past smoking on the risks of lung cancer in ex-smokers. 17th International Workshop on Statistical Modeling, Chania, Greece, July 2002.
55. Parent M-É, Siemiatycki J, Desy M. Exposure to chemical agents during leisure activities and risk of non-Hodgkin's lymphoma. Inter. Epidemiology Association, Montréal, August 2002.
56. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. International Epidemiological Association (IEA), World Congress of Epidemiology, Montréal, Québec, August 2002.
57. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Exposure-response relationships between cigarette smoking and male lung cancer from a case-control study in Montréal: generalized additive model approach. International Epidemiology Association (IEA) XVI World Congress of Epidemiology. Montréal, Québec. August 2002.
58. Parent M-É, Rousseau M-C, Siemiatycki J, Desy M. Body mass index and male cancer incidence at twelve different sites. Body mass index and male cancer incidence at twelve different sites. Halifax, Nova Scotia, June 2003.
59. Desautels N, Siemiatycki J, Parent M.E. Association between lifetime consumption of coffee, tea, and soft drinks, and incidence of eleven types of cancer: a case-control study. CSEB 2003 Biennial Meeting. Halifax, Nova Scotia, June 2003.
60. Parent M-É, Siemiatycki J, Desy M. Association between beta-carotene intake and risk of cancer at several sites. Society for Epidemiologic Research, Atlanta, Georgia, June 2003.
61. Parent M-É, Siemiatycki J, Laplante O, Desy M. Risk of lung cancer and mesothelioma associated with occupational exposure to Asbestos: A population-based case-control study in Montréal, Canada. International Society for Environmental Epidemiology, Perth, Australia, September 2003.
62. Parent M-É, Siemiatycki J, Laplante O, Désy M. Occupational exposure to asbestos and risk of lung cancer and mesothelioma: results from a population-based-case-control study in Montréal. CARWH Conference. Montréal, Québec, October 2003.
63. Parent M-É, Siemiatycki J, Latreille B, Désy M. Lifetime Occupational Physical Activity and Prostate Cancer Risk. Society for Epidemiologic Research. Salt Lake City, Utah, June 2004.
64. Parent M-É, Rousseau M.C, Siemiatycki J, Boffetta P, Cohen A. Contrasting evidence when using hospital or population controls: the example of the association between exposure to gasoline and diesel exhaust, and lung cancer. 16th conference of the International Society for Environmental Epidemiology (ISEE). New York City, August 2004.
65. De Guire L, Lebel G, Gingras S, Levesque B, Camus M, Provencher S, Case B, Langlois A, Laplante O, Siemiatycki J, Lajoie P. Epidemiology of Asbestos-related diseases in Québec, Canada. EPICOH 2004. Melbourne, Australia, October 2004.
66. Richardson H, Aronson K, Parent M-É, Siemiatycki J. Risk of cancer due to occupational exposure to six types of chlorinated hydrocarbons. EPICOH, Melbourne, Australia, October 2004.

67. De Guire L, Lebel G, Gingras S, Levesque B, Camus M, Provencher S, Case B, Langlois A, Laplante O, Siemiatycki J, Lajoie P. Épidémiologie des maladies reliées à l'exposition à l'amiante au Québec. Board Meeting, Canadian Association of University Teachers. Ottawa, November 2004.
68. Rousseau M-C, Parent M-É, Siemiatycki J. Occupational exposure to lead and risk of cancer in a population-based case-control study from Montréal, Canada. Canadian Association for Research on Work and Health, Vancouver, May 2005.
69. Parent M-É, Rousseau M-C, Siemiatycki J, Desy, M. Using proxy respondents when assessing occupational circumstances in a case-control study of cancer: For better or for worse? Canadian Association for Research on Work and Health, Vancouver, May 2005.
70. *Momoli F, Siemiatycki J, Parent M-É, Abrahamowicz M. Semi-Bayes modeling in a study of lung cancer and multiple occupational chemicals: Comparison of results for five suspected lung carcinogens. Canadian Association for Research on Work and Health, Vancouver, May 2005.
71. *Momoli F, Siemiatycki J, Parent M-É, Abrahamowicz M. Semi-Bayes models: An empirical comparison of modeling approaches in a study of lung cancer and occupational chemicals. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
72. Rousseau M-C, Camus M, Case B, Siemiatycki J. Incidence of pleural mesothelioma among women in Québec, 1970-1989: A comparison between asbestos mining and non-mining areas. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
73. Leffondre K, Abrahamowicz M, Siemiatycki J. Modeling smoking history using an overall indicator of exposure. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
74. Parent M-É, Siemiatycki J, Latreille B, Desy M. Is occupational physical activity associated with cancer risk among men? Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
75. *Ramanakumar AV, Parent M-É, Menzies R, Camus M, Siemiatycki J. Previous history of lung disease and risk of lung cancer in Montréal. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
76. *Benedetti A, Parent M-É, Siemiatycki J. Alcohol consumption and lung cancer risk in two case-control studies in Montréal, Canada. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
77. Leffondre K, Abrahamowicz M, Siemiatycki J. Modeling smoking history using an overall indicator of exposure. 26th Annual Conference of the International Society for Clinical Biostatistics (ISCB), Szeged, Hungary, August 2005.
78. Rousseau M.-C, Parent M-É, Siemiatycki J. Exposition professionnelle au plomb et risque de cancer : Étude de cas-témoin basée sur la population de Montréal, Qc. Environnement et santé : Congrès international de l'Association des épidémiologistes de langue française (ADELF), Québec, September 2005.
79. *Ramanakumar AV, Parent M-É, Siemiatycki J. Residential fuel exposures and risk factors for lung cancer: Evidence from two population-based case-control studies in Montréal. Spring Colloquium: Environmental Health Research Network (RRSE), Montréal, May 2006.
80. Sharek M, Rousseau M-C, Siemiatycki J, Parent M-É. Antioxydants et prévention du cancer du poumon : où en sommes-nous? Spring Colloquium: Environmental Health Research Network (RRSE), Montréal, May 2006.
81. Parent M-É, Shareck M, Désy M, Rousseau M-C, Siemiatycki J. Night Work and Risk of Prostate and Colon Cancers. Second North American Congress of Epidemiology, Seattle, June 2006.
82. Rousseau M-C, Parent M-É, Siemiatycki J. Exposure to lead compounds, occupation, and risk of cancer. Second North American Congress of Epidemiology, Seattle, June 2006.
83. *Ramanakumar AV, Parent M-É, Siemiatycki J. Risk of lung cancer from traditional heating and cooking fuels in Montréal. 2006 American Association for Cancer Research (AACR) International Conference on Frontiers in Cancer Prevention Research, Boston, November 2006.

84. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-E. Antioxydants et prévention du cancer du poumon: où en sommes-nous? Second Conference of the Association des étudiantes et étudiants en Santé Publique de l'Université de Montréal, Montréal, February 2007.
85. *Liu A, Abrahamowicz M, Siemiatycki J. Selected Methodological Issues in Testing and Estimating Sex Interactions with Multi-dimensional Exposures: a Simulation Study. 3rd Annual GENESIS (Gender and Sex Determinants of Cardio-vascular Disease: From Bench to Beyond) Montréal Meeting, Montréal, March 8-9, 2007.
86. *Ramanakumar AV, Parent M-É, Siemiatycki J. Exposure to painting-related occupations and risk of lung cancer: results from two case-control studies in Montréal. Oral presentation, Canadian Society for Epidemiology and Biostatistics, Calgary, May 2007.
87. Parent M-É, Rousseau M-C, Pintos J, Nicolau B, Désy M, Siemiatycki J. Are men reporting a history of anxiety, depression or insomnia at increased risk of cancer? Annual Meeting of the Canadian Society for Epidemiology and Biostatistics, Calgary, May 2007.
88. *Pintos J, Parent M-É, Rousseau M-C, Siemiatycki J. Risk of mesothelioma associated with occupational exposure to asbestos: Evidence from two case-control studies in Montréal, Canada. Annual Meeting of the Canadian Society for Epidemiology and Biostatistics, Calgary, May 2007.
89. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Dietary antioxidants intake and risk of lung cancer: A population-based case-control study. Poster presentation, 2007 CSEB Student Conference, Calgary, Alberta, May 2007.
90. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Dietary antioxidants intake and risk of lung cancer: a population-based case-control study. Poster presentation, Spring 2007 Conference of the Environmental Health Research Network (RRSE-FRSQ), Montréal, May, 2007.
91. Parent M-É, Rousseau M-C, Pintos J, Nicolau B, Désy M, Siemiatycki J. Is there a link between stress at work and cancer risk? Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007;165(11)Suppl:S3.
92. Nicolau B, Parent M-É, Rousseau M-C, Désy M Siemiatycki J. Childhood socioeconomic position in relation to cancer: evidence from a Canadian population based case-control study. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007;165(11)Suppl:S77.
93. *Pintos J, Parent M-É, Rousseau M-C, Siemiatycki J. Occupational Exposure to Asbestos and Man-Made Vitreous Fibers, and Risk of Lung Cancer: evidence from two case-control studies in Montréal, Canada. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007; 165(11) Suppl: S102.
94. Rousseau M-C, Parent M-É, Desy M, Siemiatycki J. History of allergic disease and risk of cancer. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007;165(11)Suppl:S100.
95. *Momoli F, Parent M-É, Abrahamowicz M, Nadon L, Lakhani, Latreille B, Krewski D, Siemiatycki J. Lung cancer risk from selected occupational chemicals. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007; 165(11)Suppl:S102.
96. *Momoli F, Parent M-É, Abrahamowicz M, Nadon L, Lakhani, Latreille B, Krewski D, Siemiatycki J. Lung cancer risk from selected occupational chemicals. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007; 165(11) Suppl: S102.
97. *Liu A, Abrahamowicz M, Siemiatycki J. Testing and estimating interactions with multi-dimensional exposures: A simulation study. 28th Annual Conference of the International Society for Clinical Biostatistics, Alexandroupolis, Greece, July-August 2007.
98. Parent M-E, Rousseau M-C, Siemiatycki J, Goldberg M, Aprikian F, Saad F, Karakiewicz P. Main determinants of response rates in a large population-based case-control study of environmental, lifestyle and genetic factors, and prostate cancer in Montréal, Canada. Making Connections: A Canadian Cancer Research Conference, Toronto, November 15-17, 2007.
99. *Liu A, Abrahamowicz M, Siemiatycki J. Testing and estimating interactions with multi-dimensional exposures: A simulation study. 10e Congrès annuel des étudiants, stagiaires et résidents du centre de recherche du CHUM. Montréal, December 18, 2007.

100. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Fruit and vegetables, and risk of lung cancer, by smoking intensity. Society for Epidemiologic Research, Chicago, June 2008.
101. Parent M-É, Siemiatycki J, Goldberg M, Désy M. Birth weight, obesity during childhood, adolescence and adulthood, and prostate cancer - Preliminary data from the PROTEuS study. Society for Epidemiologic Research, Chicago, June 2008. *American Journal of Epidemiology* 2008 ; 167 (Suppl.): S62
102. Leffondré K, Wynant W, Cao Z, Siemiatycki J. A comprehensive smoking index to model smoking history in cancer studies. Society for Epidemiologic Research, Chicago, June 2008.
103. *Beveridge R, Pintos J, Parent M-É, Asselin J, Siemiatycki J. Risk of lung cancer after occupational exposure to cadmium, chromium VI, and nickel. Society for Epidemiologic Research, Chicago, June 2008.
104. *Liu A, Abrahamowicz M, Siemiatycki J. Methodological challenges in testing and estimating interactions with multi-dimensional exposures. Society for Epidemiologic Research, Chicago, June 2008.
105. Leffondré K, Wynant W, Cao Z, Abrahamowicz M, Siemiatycki J. A weighted Cox model for case-control data with time-dependent exposures. 29th Annual Conference of the International Society for Clinical Biostatistics, Copenhagen, August 17-21, 2008.
106. Koushik A, Parent M-É, Siemiatycki J. Characteristics of menstruation and pregnancy and the risk of lung cancer in women. 6th Annual American Association for Cancer Research, Frontiers in Cancer Prevention Research Meeting, Philadelphia, November 16-19 - 2008
107. Olsson A.C., Gustavsson P, Kromhout H, Siemiatycki J, et al. Pooled Analyses on Diesel Motor Exhaust and Lung Cancer in Europe and Canada. Poster presentation. 29th ICOH International Congress on Occupational Health, Cape Town, South Africa, March 2009.
108. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Dietary Intake of Antioxidants and Risk of Four Histological Subtypes of Lung Cancer: a Population Based Case-Control Study. Oral presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) and Association of Public Health Epidemiologists in Ontario (APHEO) Joint Conference, Ottawa, Ont. May 2009
109. Nkosi MT, Rousseau M-C, Parent M-É, Siemiatycki J. Comparison of indicators of financial situation in the context of an epidemiological study. Poster presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) and Association of Public Health Epidemiologists in Ontario (APHEO) Joint Conference, Ottawa Ont, May 2009.
110. Nkosi MT, Rousseau M-C, Parent M-É, Siemiatycki J. Studying socio-economic status and lung cancer risk; How important Is the modelling of smoking? Poster presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) Student Conference, Ottawa Ont, May 2009.
111. Rousseau M-C Parent M-E, Nicolau B, Koushik A, Siemiatycki J. Body mass index and lung cancer risk in a population-based case-control study from Montréal, Canada. Poster presentation at the 42nd Annual Meeting of the Society for Epidemiological Research (SER) Meeting Anaheim Ca, June 23-26 2009.
112. *Pintos J, Parent M-E, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer; evidence from case-control study in Montréal. Oral presentation. 42nd Annual Meeting of the Society for Epidemiologic Research Meeting (SER), Anaheim, June 23-26 2009.
113. *Perron S, Jacques L, Siemiatycki J, Ducharme F. Home multifaceted environmental interventions to improve asthma control: A systematic review. 137th Annual Meeting of the American Public Health Association (APHA), November 7-11 2009, Philadelphia, PA.
114. *Wynant W, Siemiatycki J, Parent M-E, Rousseau M-C. Exposition professionnelle au plomb et risque de cancer du poumon. Présentation orale, Congrès Armand Frappier, Bromont (Qc), Novembre 2009.
115. Kâ K, El-Zein M, Parent M-É, Siemiatycki J, St-Pierre Y, Rousseau M-C. Antécédent médical d'asthme ou d'eczéma et risque de cancer: une étude cas-témoins à base populationnelle. Présentation orale, Congrès Armand Frappier, Bromont (Qc), Novembre 2009.
116. Soskolne CL, Jhangri GS, Scott HM, Brenner DR, Siemiatycki J, Lakhani RA, Gérin M, Dewar R, Miller AB, Risch H. A population based case-control study of occupational exposure to acids and the risk of lung cancer: evidence for specificity with laryngeal cancer. Poster presentation at INSIGHTS'09, School of Public Health, University of Alberta, Edmonton, Alberta, November 12 2009.

117. *Pintos J, Lavoué L, Van Tongeren M, Kauppinen T, Richardson L, Sleguwenhoek A, Lakhani R, Cardis E, Siemiatycki J. Comparison of exposure estimates in FINJEM with expert-based assessments performed in Montréal. Part I: Exposure prevalence. Oral presentation. Epidemiology in Occupational Health (EPICOH), Taipei, April 2010.
118. Lavoué J, Pintos J, Van Tongeren M, Kauppinen T, Richardson L, Sleguwenhoek A, Lakhani R, Cardis E, Siemiatycki J. Comparison of exposure estimates in FINJEM with expert-based assessments performed in Montréal. Part II: Exposure levels. Oral presentation. Epidemiology in Occupational Health (EPICOH), Taipei, April 2010.
119. *Christensen KY, Naidu A, Parent M-E, Pintos J, Siemiatycki J, Koushik A. The risk of lung cancer related to dietary intake of flavonoids. Annual Meeting of the Society for Epidemiologic Research (SER), Seattle, Washington, June 2010.
120. *Wynant W, Siemiatycki J, Parent M-E, Rousseau M-C. Occupational exposure to lead compounds and lung cancer. SER, Seattle, June 2010.
121. *Liu A, Abrahamowicz M, Siemiatycki J. Methodological challenges in testing and estimating interactions with multi-dimensional exposures. Annual Meeting of the Society for Epidemiologic Research (SER), Seattle, June 2010.
122. Rousseau M-C, Conus F, Parent M-É, Siemiatycki J. History of allergic diseases and risk of lung cancer. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
123. Leffondré K, Wynant W, Cao Z, Siemiatycki J. A comprehensive smoking index to model smoking history in cancer studies. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
124. *Liu A, Abrahamowicz M, Siemiatycki J. When Interaction Estimates in Logistic Regression are Confounded? Oral presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
125. *Vallières É, Siemiatycki J, Lavoué J, Pintos J, Parent M-E. Risk of lung cancer after exposure to welding fumes in two population-based case-control studies. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
126. *Mahboubi A, Koushik A, Siemiatycki J, Lavoué J, Rousseau M-C. Occupational exposure to formaldehyde and risk of lung cancer. Poster presentation Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):762-S.
127. *Mahboubi A, Abrahamowicz M, Siemiatycki J. Simulation study of multiple logistic regression estimates for multiple correlated exposures measured with errors. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
128. *Al-Zoughool M, Pintos J, Richardson L, Parent M-É, Ghadirian P, Krewski D, Siemiatycki J. Exposure to environmental tobacco smoke and risk of lung cancer: evidence from a case-control study in Montréal, Canada. Poster presentation. Third North American Congress of Epidemiology, Montréal, Quebec, Canada, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
129. El-Zein M, Parent M-É, Nicolau B, Koushik A, Siemiatycki J, Rousseau M-C. Smoking, body mass index and lung cancer risk. Poster presentation. Third North American Congress of Epidemiology, Montréal, Quebec, Canada, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
130. Karp I, Abrahamowicz M, Leffondré K, Siemiatycki J. Development of a method for assessment of risk of lung cancer. Poster presentation. Third North American Congress of Epidemiology, Montréal, Quebec, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
131. Momoli F, Parent M-E, Siemiatycki J, Platt R, Richardson L, et al. A probabilistic multiple-bias model applied to a study of mobile phone use and risk of glioma. Third North American Congress of Epidemiology, Montréal, Quebec, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
132. Siemiatycki J, Richardson L, Kincl L, Schlaefel K, Cardis E. Oral presentation. INTEROCC Study: Social Class and The Risk of Glioma Brain Tumours. International Society for Environmental Epidemiology (ISEE), Barcelona, Spain, September 2011.

133. Siemiatycki J, Richardson L, Kincl L, Schlaefter K, Cardis E. Oral presentation. INTEROCC Study: Social Class and The Risk of Meningioma Brain Tumours. International Society for Environmental Epidemiology (ISEE), Barcelona, Spain, September 2011.
134. Kendzia B, Pesch B, Jöckel K.-H, Kromhout H, Straif K, Brüning T, on behalf of the SYNERGY Working Group. Lung cancer risks of welding in a pooled analysis of case-control studies. Oral presentation. 7th International Conference on Science of Exposure Assessment (X2012), Edinburg, Scotland, July 2012.
135. Olsson A.C, Vlaanderen J, Vermeulen R, Kromhout H, Pesch B, Straif Kurt on behalf of the SYNERGY study Group. Improved risk estimation through advanced exposure modelling in community-based studies: the example of occupational asbestos exposure in the SYNERGY project. Oral presentation. 7th International Conference on Science of Exposure Assessment (X2012), Edinburgh, Scotland, July 2012.
136. *Lacourt A, Lavoué J, Labrèche F, Siemiatycki J. Gender differences in occupational exposures assessed by experts in a community based-case control study of lung cancer. Oral presentation 7th International Conference on the Science of Exposure (X2012), Edinburgh, Scotland, July 2012.
137. *Pasquet R, Karp I, Siemiatycki J, Koushik A. Intake of black tea and coffee and the risk of lung cancer. E-poster. UICC World Cancer Congress, Montréal, Quebec, 27-30 August 2012.
138. *Vallièrès E, Siemiatycki J, Lavoué J, Pintos J, Parent M-E. Risk of three histological types of lung cancer after exposure to welding fumes. Poster presentation, UICC World Cancer Congress, Montréal, Quebec, 27-30 August 2012.
139. *Rivera M, *Vizcaya D, Pintos J, Abrahamowics M, Siemiatycki J. Association between exposure to engine emissions and lung cancer. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
140. *Vizcaya D, Lavoué J, Bégin D, Pintos J., Richardson L, *Rivera M, Siemiatycki J. Risk of eight types of cancer and cleaning-related exposures in a case-control study. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
141. *Vizcaya D, Lavoué J, Pintos J, Richardson L, Siemiatycki J. Lung cancer and cleaning-related exposures: results from two case-control studies. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
142. Turner M-C, Benke G, Bowman J, et al. Occupational exposure to extremely low frequency magnetic fields and brain tumour risks in the INTEROCC study. Environment and Health – Joint meeting of the International Society for Environmental Epidemiology (ISEE), the International Society for Exposure Sciences (ISES) and the International Society for Indoor Air Quality (ISIAQ), Basel, Switzerland, 19-23 August 2013.
143. Lavoué J, Labrèche F, Richardson L, Goldberg M, Parent M-E, Siemiatycki J. CANJEM: a general population job exposure matrix based on past expert assessments of exposure to over 250 agents. 24th International Conference on Epidemiology in Occupational Health (EPICOH), Chicago, Illinois, 24-27 June 2014. [abstract] Occupational & Environmental Medicine. 2014;71 (Suppl 1):A48.
144. *Ho V, Parent M-E, Pintos J, Abrahamowicz M, Gauvin L. Siemiatycki J, Koushik A. Lifetime occupational physical activity and lung cancer risk. 17^{ème} Congrès des étudiants, stagiaires et résidents du CRCHUM, Montréal, Quebec, December 2014.
145. Turner M C, Sadetzki S, Eastman Langer C, Figuerola J, Armstrong BK, Chetrit A, Giles GG, Krewski D, Hours M, McBride /ML, Parent M-E, Richardson L, Siemiatycki J, Woodward A, Cardis E. Impact of case:control matching strategies on associations between cellular telephone use and glioma risk in the INTERPHONE study. International Society for Environmental Epidemiology (ISEE), Seattle, Washington, 25 August 2014.
146. *Dutczak H, Siemiatycki J, Koushik A. Exposure to stressful life events and lung cancer risk. 10^{ème} Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Quebec, February 2015.
147. *Xu M, Richardson L, Campbell S, Siemiatycki J. Trends and Characteristics of Response Rates in Case-Control Studies of Cancer. 10^{ème} Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Montréal, Quebec, February 2015.

148. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. L'association entre l'exposition occupationnelle aux métaux et le cancer du cerveau. 10ème Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Montréal, Quebec, February 2015.
149. *Dutczak H, Siemiatycki J, Koushik A. Stressful life events and lung cancer risk. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
150. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. The association between occupational exposure to metals and metalloids and brain cancer risk. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
151. *Xu M, Richardson L, Campbell S, Siemiatycki J. Trends and Characteristics of Response Rates in Case-Control Studies of Cancer. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
152. Behrens T, Groß I, Siemiatycki J, Conway D, Jöckel K-H, Olsson A, Kromhout H, Straif K, Schüz J, Hovanec J, Kendzia B, Pesch B, Brüning T. Niedriges berufliches Prestige, soziale Mobilität und Lungenkrebs – die SYNERGY-Studie. German Epidemiology Association (DGEpi), Potsdam, Germany, September 2015.
153. *Carrier M, Kestens Y, Siemiatycki J. Nuisances environnementales et risques pour la santé. AQTR, Montréal, Quebec, 15 September 2015.
154. *Sauvé JF, Siemiatycki J, Labrèche F, Lavoué J. Development of the CANJEM job exposure matrix: Bayesian modelling of occupational exposures assigned by experts to over 30000 jobs spanning 1920-2005. The International Society of Exposure Science (ISES), Henderson, Nevada, 18-22 October 2015.
155. Vila J, Bowman JD, Richardson L, Kincl L, Conover D, van Tongeren M, Mann S, Vecchia P, McLean D, Cardis E, on behalf of the INTEROCC Study Group. Assessing cumulative exposures to electromagnetic fields: From source-based measurements to individual lifetime exposure estimates. The International Society of Exposure Science (ISES) Henderson, Nevada, 18-22 October 2015.
156. *Karumanchi S, Hatsopoulou M, Richardson L, Siemiatycki J. Methodology for exposure assessment for UFPs in the Grand Montréal Region. Oral presentation. 11th Annual Symposium of the Student Association in Public Health at the Université de Montréal (AÉÉSPUM), Montréal, Quebec, 9 February 2016.
157. *Carrier M, Apparicio P, Kestens Y, Séguin AM, Pham H, Crouse D, Siemiatycki J. Application of a global environmental equity index in Montréal: diagnostic and further implications, AAG, San Francisco, California, 30 March 2016.
158. *Carrier M, Apparicio P, Kestens Y, Séguin A-M, Pham H, Crouse D, Siemiatycki J. Application d'un indice d'équité environnementale à Montréal: établissement d'un diagnostic pour cibler les secteurs et les groupes les plus vulnérables, ACFAS, Montréal, Quebec, 11 May 2016.
159. *Carrier M, Kestens Y, Crouse D, Siemiatycki J. Lung cancer and exposure to Nitrogen Dioxide and Traffic in Montréal, World Conference on Transport Research, Shanghai, China, 10 July 2016.
160. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Patterns and trends in quality of response rate reporting in case-control studies of cancer. 18th Congress of Students, Interns and Residents of CRCHUM, Montréal, Quebec, 4 May 2016.
161. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Time trends and study design determinants of response rates in case-control studies of cancer. 18th Congress of Students, Interns and Residents of CRCHUM, Montréal, Quebec, 4 May 2016.
162. *Karumanchi S, Hatsopoulou M, Richardson L, Thierry B, Goldberg M, Siemiatycki J. Land use regression model of UFPs in the Grand Montréal Region. Oral presentation. Canadian Society for Epidemiology and Biostatistics, Winnipeg, Manitoba, 8-10 June 2016.
163. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Subject response rates in case-control studies of cancer: quality of reporting, time trends, and study design determinants. Epidemiology Congress of the Americas, Miami, Florida, 21-24 June 2016.
164. *Rémen T, Siemiatycki J, Lavoué J. Impact of inter-coder differences in occupation and industry classification coding on exposure estimates obtained via job-exposure matrix: example of gasoline engine

- emissions in CANJEM. Oral presentation. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
165. *Sauvé JF, Lavoué J, Siemiatycki J, Parent ME. Evaluation of a hybrid expert approach for retrospective assessment of occupational exposures in a population-based study of prostate cancer in Montréal, Canada. Oral presentation. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
 166. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. The association between occupational exposure to metals and metalloids and brain cancer risk. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
 167. Russ D, Rémen T, Ho KY, Chow WH, Davis F, Hofmann J, Huang H, Purdue M, Schwartz K, Siemiatycki J, Zhang Y, Silverman D, Johnson C, Lavoué J, Friesen M. Recommendations for prioritizing expert review of free-text job descriptions that underwent computer-based coding using the SOCcer algorithm. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
 168. *Sauvé JF, Labrèche F, Richardson L, Goldberg MS, Parent MÉ, Siemiatycki J, Lavoué J. Development of the CANJEM Canadian general-population job-exposure matrix from past expert evaluations. Oral presentation. Canadian Association for Research on Work and Health (CARWH) conference, Toronto, Ontario, October 2016.
 169. *Rémen T, Siemiatycki J, Lavoué J, Verner MA. Impact of inter-coder differences in occupation and industry classification coding on exposure estimates obtained via job-exposure matrix: example of gasoline engine emissions in CANJEM. Poster. International Society of Exposure Science (ISES) 2016 Annual Meeting, Utrecht, Netherlands, 9-13 October 2016.
 170. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. Lifetime recreational moderate-to vigorous physical activity and the risk of ovarian cancer by subtype. Poster presentation. 2016 American Institute for Cancer Research (AICR) Research Conference, North Bethesda, Maryland, 14-16 November 2016.
 171. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. The impact of menopausal status on the association between moderate-to-vigorous physical activity among participants in the Prevention of OVarian Cancer in Quebec (PROVAQ) study. Oral Presentation. Canadian Society for Epidemiology and Biostatistics 2017 Biennial Conference, Banff, Alberta, 1 June 2017
 172. Bowman JD, Vila J, Richardson L, Kincl L, Cardis E on behalf of the INTEROCC Study Group. Occupational Exposures to Radio-frequency Electric Fields Assessed for the INTEROCC Study of Brain Cancer. Oral presentation. American Industrial Hygiene Association conference, Seattle, Washington, 4-7 June 2017.
 173. *Karumanchi S, Siemiatycki J, Hatzopoulou M. Some challenges in measuring ultra-fine particles and developing a land use regression model. Oral presentation. Canadian Society for Epidemiology and Biostatistics (CSEB) 2017 Biennial Conference, Banff, Alberta, 30 May 2017.
 174. *Sauvé JF, Davies HW, Parent MÉ, Peters CE, Siemiatycki J, Sylvestre MP, Lavoué J. Development of quantitative estimates of wood dust exposure in a Canadian general population job-exposure matrix based on past expert assessments. 26th Conference on Epidemiology in Occupational Health (EPICOH 2017), Edinburgh, Scotland, August 2017.
 175. Ho V, Xu M, Pintos J, Lavoué J, Abrahamowicz M, Rousseau M.C, Richardson L, Siemiatycki J. Occupational exposures to leaded and unleaded gasoline engine emissions and lung cancer risk. Canadian Cancer Research Conference, Vancouver, British Columbia, 5-7 November 2017.
 176. Lequy E, Siemiatycki J, Leblond S, et al. Moss biomonitoring as an alternative to assess exposure to atmospheric metals in environmental epidemiology: the example of the bramm network and the gazel cohort. Poster. SEE Young 2018, Early Career Researchers Conference on Environmental Epidemiology – Together for a Healthy Environment, Freising, Germany, 19–20 March 2018. Occup Environ Med 2018;75:A27.
 177. Ho V, Parent MÉ, Lavoué J, Zhu Y, Siemiatycki J, Koushik A. Gender Differences in Occupational Physical Activity. Oral presentation. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario. 26-30 August 2018.

178. *Xu M, Ho V, Siemiatycki J. Association between occupational exposure to textile fibre dusts and lung cancer in a population-based case-control study in Montréal: a preliminary analysis comparing results from three analytical methods. Oral presentation. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
179. Zhu Y, Lavoué J, Parent MÉ, Siemiatycki J, Koushik A, Ho V. Occupational Physical Activity and Lung Cancer Risk among Participants of the Alberta's Tomorrow Project. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
180. *Karumanchi S, Siemiatycki J, Richardson L, Hatzopoulou M. Estimating exposure to Ultrafine Particles in the Greater Montreal Area among case-control study subjects: Comparison of classical land use regression model with a model based on Bayesian principles - Proposal. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
181. van Tongeren M, Dirkx E, Lavoué J, Siemiatycki J, Ho V. Assessment of Occupational Exposure to Endocrine Disrupting Agents. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.

* First author was under supervision of J. Siemiatycki when this work was carried out

GRANTS AND CONTRACTS RECEIVED

1. Comparison of three methods for conducting household health surveys; Nat. Health Res & Devel. Prog. (NHRDP); \$27,000; 1974-76.
2. Pilot study of a case-control monitoring system for discovering occupational carcinogens; Conseil de la recherche en santé (CRSQ); \$80,000; 1978-1980.
3. Établissement du jeune chercheur; CRSQ; \$15,000; 1979-80.
4. Analyse de santé auprès de 1600 ménages montréalais; Ministère des affaires sociales (MAS); \$12,708; 1980
5. Dépistage des facteurs cancérigènes de l'environnement professionnel montréalais: étude pilote; Commission des accidents du travail; \$59,093 ; 1980-82.
6. Registry of patients with Juvenile Onset Diabetes in Québec; NHRDP; \$35,478*; 1980-85; (P.I. Dr E. Colle).
7. Secondary analysis of a health survey in Montréal: methodologic issues and comparison of morbidity and health care utilization between social groups; NHRDP-H&W Can.; \$15,000; 1981-82.
8. Exposure-based case-control approach to discovering occupational carcinogens; NHRDP-H&W Can.; \$129,258; 1981-83.
9. An exposure-based case-control approach to discovering occupational carcinogens; NCIC; \$131,842; 1981-83.
10. Variation in sex ratios of cancer between geographic areas; NCIC; \$3,227; 1982-84.
11. Équipe associée en épidémiologie des cancers professionnels (Team grant); Institut de la recherche en santé et sécurité du travail (IRSST); \$1 120,000; 1982-85.
12. Formaldehyde et cancer; IRSST; \$9,500; 1983.
13. Retrospective cohort study in the Montréal fur industry; IRSST; \$34,019; 1983-85.
14. Statistical analysis of a case-control study designed to discover occupational carcinogens; NHRDP-H&W Can.; \$484,022; 1985-87.
15. Completion of chemical coding of exposures in a case-control study designed to discover occupational carcinogens; IRSST; \$102,180; 1986.
16. Risks of cancer due to exposure to asbestos in a range of occupations; IRDA; \$61,206; 1986-87.
17. Biological estimation of exposure: a tissue registry for the identification and quantification of occupational carcinogens; NCIC; \$3,500*; 1986-87; (P.I. Dr B. Case)
18. Development of a proposal to study cancer risk and non-occupational exposure to asbestos; H&W Can.; \$29,500; 1987-88.
19. Evaluation of cancer risk and occupational exposure to formaldehyde; H&W Can.; \$30,000; 1987-88.
20. A genetic-epidemiologic study of breast cancer; NIH-NCI; \$90,945(US)*; 1987-92; (P.I. Dr. R. Haile).

21. Scholar award; NHRDP-H&W Can.; \$298,689; 1987-93.
22. An intervention trial to assess the risks of gastro-intestinal illness associated with consumption of treated tap water; NHRDP; \$225,000*; 1987-89; (P.I. Dr P. Payment).
23. Evaluation of cancer risk and occupational exposure to polycyclic aromatic hydrocarbons; H&W Can.; \$29,500; 1988-89.
24. Evaluation of cancer risk and occupational exposure to benzene, toluene and xylene; H&W Can, \$40,000; 1988-89.
25. Health risks due to chrysotile asbestos in the non-occupational environment: a workshop to evaluate a research protocol; H&W Can, \$20,000; 1988-89.
26. A population-based, case-control study of occupational exposure to sulphuric acid and the development of laryngeal cancer: an augmented secondary data analysis; NHRDP; \$11,120*; 1988-89; (P.I. Dr. C. Soskolne).
27. Mortality due to asbestos in the general environment of the Quebec mining areas; H&W Can.; \$130,000; 1989-90.
28. A case-control approach to discovering occupational carcinogens: an analysis of data; NHRDP; \$55,508; 1989-90.
29. Continued analysis of a large case control study of many types of cancer: occupational and non-occupational risk factors; NHRDP; \$463,827 1988-1992
30. Risk of cancer due to cigarette smoking - results of a multi-site case-control study; H&W Can.; \$30,000; 1989-90.
31. Étude sur la validité de matrice emploi-expositions multisectorielles; IRSST; \$18,207*; 1990-1992; (P.I. Dr. M. Gérin).
32. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; \$526,297; 1990-1994.
33. Leukemia in children due to parental occupational exposures; NHRDP; \$108,000*; 1990-1994; (P.I. Dr Claire Infante-Rivard).
34. Risk of cancer due to exposure to chlorinated solvents - results of a multi-site case-control study; H & W Can.; \$30,000; 1991-92.
35. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer retrospective assessment of exposure; H & W Can.; \$60,000; 1991-92.
36. Feasibility of epidemiologic methods to investigate health outcomes near waste sites; H & W Canada; \$33,000; 1991-92
37. A pilot study to evaluate the prevalence of hip arthritis in the Montréal urban setting, and an evaluation of methods of recruitment of a population aged 65+; Montréal General Hospital Clinical Epidemiology; \$15,000*; 1991-92; (P.I. Dr. J. Esdaile).
38. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer; mesothelioma ascertainment; NHRDP; \$164,000; 1991-95.
39. Multivariate Regression Analyses of Occupational Risk Factors for Several Types of Cancers; NHRDP; \$128,827; 1992-96.
40. Development of a Job-Exposure Matrix for Use in Epidemiologic Case-Control Studies of Occupational Risk Factors; NHRDP; \$85,003; 1992-95.
41. A prospective epidemiological study of gastrointestinal health effects due to consumption of drinking water. E.P.A. (US)/ NHRDP/ Nat. Water Res. Inst.; \$300,000*; 1993-95. (P.I.: Dr. P. Payment)
42. A population-based, case-control study of occupational exposure to acidifying agents and the development of lung cancer: an augmented, secondary data analysis. NHRDP; \$72,220*; 1993-1995. (P.I. Dr. C. Soskolne).
43. Scholar award; NHRDP-Health Canada; \$126,990; 1993-95.
44. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; \$242,652; 1994-1998.
45. Examen pathologique de cas présumés de mésothéliome recensés chez des femmes depuis 1970 dans des hôpitaux du québec. Health and Welfare Canada. \$30,000. 1994.

46. Cohort Study of a Ten Percent Sample of the Canadian Labour Force. NHRDP; \$12,000*; 1994-97. (P.I. Dr. K. Aronson)
47. A health survey of persons living near the Miron Quarry Sanitary Landfill site, Montréal: a pilot study. NHRDP; \$88,931 ; 1994-95. (P.I. Dr. M. Goldberg)
48. Occurrence of pathogenic microorganisms in water from St Laurent hydrological basin. FRSQ/ NHRDP & St Laurent Vision 2000; 1995-97. (P.I. P Payment)
49. Case-control study of lung cancer and environmental tobacco smoke; Health Canada; \$544,344; 1995-1997.
50. Case-control study of lung cancer and occupational exposures: NHRDP; \$840,000.; 1995–1998.
51. Occupational exposure to solvents and risk of breast cancer; National Cancer Institute of Canada; \$300,000*; 1995-1997. (P.I.: M Goldberg).
52. Scholar Award; NHRDP-Health Canada; \$263,329, 1995-1998.
53. Reanalysis of US data relating general mortality to air pollution; Health Effects Institute; 1998-2000 (P.I. D Krewski)
54. A case-control study of occupational risk factors for lung cancer; Medical Research Council of Canada; \$554,757, 1998-2001
55. Évaluation du risque de cancer du poumon et de mésothéliome associé à l'exposition à l'amiante chez les travailleurs de la région montréalaise; Ministère de la Santé et des Services sociaux; \$12,000. 1998.
56. Feasibility of a case-control study of the association between cell phone use and brain, salivary gland cancer and acoustic neurinoma. International Agency for Research on Cancer; \$12,000, 1998.
57. Inorganic particulate retained dose markers in lung cancer and mesothelioma. CIHR (P.I. Bruce Case) \$66,096. 1999-2003
58. Distinguished Scientist Award, Medical Research Council of Canada; \$330,000; 1999-2004.
59. Évaluation du risque de mésothéliome associé à l'exposition à l'amiante chez les femmes de la région minière; Ministère de la Santé et des Services sociaux; \$27,500. 1999-2000.
60. Program of research in environmental epidemiology of cancer (a national program to enhance capacity to conduct research) PREECAN; National Cancer Inst of Canada; \$1,000,000; 2000-2004.
61. Designing a national research agenda in environmental epidemiology of cancer. Medical Research Council of Canada Opportunities Program; \$40,000; 2000-2001.
62. Multi-centric case-control study of cell phone use and cancer risk in Montréal. CIHR; \$500,000; 2000-2004.
63. Trainee award for: Bernard Rachet, Post-doctoral fellow. PREECAN – NCIC; \$46,750; 2001-2003.
64. Cardiogene: a consortium to explore the gene-environment paradigm of major cardiovascular disorders in human and animal models. Canadian Institutes of Health Research, (P.I. P. Hamet) \$2,632,272; 2001-2007.
65. Canada Research Chair in Environmental Epidemiology. Federal CRC program. \$1,400,000; 2001-2008.
66. Installation of CRC. Canadian Foundation for Innovation. \$312,000; 2002-2004.
67. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 1). Canadian Cancer Society, Prostate Cancer Research Initiative, National Cancer Institute of Canada, (P.I. M-É Parent) \$947,360; 2002-2007.
68. Center for research on environmental etiology of cancer. For the application process. Centre Hospitalier de l'Université de Montréal (CHUM); \$7,000; 2002-2003.
69. Traffic-related air pollution and socioeconomic gradients in the incidence of cancer. CIHR, (P.I. M Goldberg) \$497,000; 2004-2007.
70. Development and validation of new statistical methods for modeling intermediate events in survival analysis. CIHR, (P.I. M Abrahamowicz) \$68,250; 2004-2005.
71. New survival analytic methods for time-dependent exposures in case-control studies, with applications to cancer. CIHR (P.I. K Leffondré) \$52,791; 2004-2007.
72. Trainee award for: Venkata Ramana Kumar, Post-doctoral fellow. PREECAN – NCIC; \$66,000; 2004-2007.

73. Environmental Cancer Research Team. Development grant for the preparation of the full team grant application. CIHR (P.I. J. Siemiatycki) \$9,500; 2005-2006.
74. Trainee award for: Franco Momoli, PhD student. PREECAN – NCIC; \$25,600; 2005-2006.
75. Occupational and selected non-occupational risk factors for lung cancer: Analysis of a case-control study in Montréal. CIHR (co-P.I.'s: J Siemiatycki & M-É Parent) \$1,920,447; 1999-2011.
76. Development and evaluation of a cost-effective approach for retrospective assessment of occupational exposures in population-based studies (pilot study). Canadian Cancer Etiology Research Network - NCIC (P.I. M-É Parent) \$35,000; 2006-2007.
77. Trainee award for: Aihua Liu, PhD student. PREECAN – NCIC; \$12,600; 2006-2007.
78. Prostate cancer and occupational whole body vibration. Ontario Workplace Insurance Board: Research Advisory Council; Solutions for Workplace Change (P.I. J Purdham); \$140,480; 2006-2008.
79. Guzzo-SRC Chair in Environment and Cancer. Cancer Research Society, \$1,285,000; 2007-2020.
80. INTEROCC: Occupational exposures and brain cancer. NIH (P.I. E Cardis: To support the analysis of the occupational component of an international case-control study involving 13 countries and coordinated at the International Agency for Research on Cancer of the WHO [France]); \$1,626,757 US; 2008-2010.
81. Development and validation of a lung cancer risk prediction model. NCIC (P.I. I Karp); \$102,099; 2008-2010.
82. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 2). NCIC (P.I.: M-É Parent); \$756,000; 2008-2011.
83. Preparation and development of an epidemiological study of modifiable and genetic factors associated with ovarian cancer risk (pilot project). Ovarian Cancer Canada (P.I.: A Koushik); \$28,330; 2008-2009.
84. SYNERGY - Pooled analysis of case-control studies on the joint effects of occupational carcinogens in the development of lung cancer: Montréal component. German Statutory Accident Insurance (DGUV) (P.I.: A Koushik); \$119,177; 2008-2010.
85. The risk of lung cancer related to occupational and recreation physical activity and to dietary intake of flavonoids. Canadian Cancer Research Society. (P.I.: A Koushik); \$208,317; 2009-2012.
86. A case-control study of modifiable and genetic factors associated with the risk of ovarian cancer. Canadian Cancer Society Research Institute (P.I: A Koushik); \$498,997; 2010- 2013.
87. Occupational and selected nonoccupational risk factors for lung cancer: analysis of a case-control study in Montréal. CIHR (P.I: J Siemiatycki, M-É Parent); \$850,620; 2011-2015.
88. Quebec Research Program for Prostate Cancer Prevention. Cancer Research Society (P.I.: M-É. Parent, P Karakiewics) \$4,728,203; 2011-2015.
89. Extreme weather and maternal-child health: targeting future impacts of climate change. CIHR. (P.I.: N Auger) \$85,333; 2015-2019.
90. Development of an instrument for assessing occupational exposures in cancer case-control studies and its application to cancers of lung, brain, ovary. Cancer Research Society- Programme GRePEC (Groupe de recherche et de prévention en environnement-cancer). (P.I.: J Siemiatycki, M Pollak) \$2,510,890; 2011-2018.
91. Occupational physical activity and lung cancer. (P.I.: V Ho, A Koushik).CIHR. \$75,000. 2017-2018.
92. Analyses of existing Canadian cohorts and databases related to occupational physical activity and lung cancer risk. CIHR. (P.I.: V Ho, A Koushik) \$74,989; 2017-2018.
93. The role of lifestyle factors in ovarian cancer prognosis. Department of Defence – Ovarian Cancer Research Program. (P.I.: A Koushik) \$216,458 USD (est. \$293, 000 CAD); 2015-2017. Extended August 2018.
94. Occupational Exposure to Endocrine Disrupting Chemicals and Colorectal Cancer risk. CIHR (P.I.: V Ho, J Siemiatycki) \$252,450; 2018-2021.
95. Occupational exposures of women: improvement of an existing job exposure matrix to provide gender-specific estimations of exposure. IRSST. (P.I.: V Ho) \$491,484; 2018-2021.

Exhibit 5

Perineal use of talc and risk of ovarian cancer

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ABSTRACT

Ovarian cancer is one of the most common gynaecological neoplasms, especially in industrialised countries. The aetiology of the disease is not well understood, except that inherited mutations in the breast cancer genes BRCA-1 and BRCA-2 account for up to 10% of all cases,¹ and child-bearing, oral contraceptive use and breast-feeding reduce the risk.² Some environmental exposures, notably talc and asbestos, have been suspected as ovarian carcinogens.

Talc refers to both mineral talc and industrial products that contain mineral talc. Mineral talc occurs naturally in many regions of the world and is valued for its softness, platyness, and ability to absorb organic matter. Mineral talc occurs naturally in a platy (flat) form, but may also occur as asbestiform fibres, which describes its physical form and does not imply the presence of asbestos. The purer forms (approximately 90% mineral talc) are used for cosmetic and hygiene products including baby powders and feminine hygiene products. Perineal use of cosmetic talc is a common practice in the United Kingdom, North America, Australia and some other countries. To our knowledge accurate estimates of prevalence of use of cosmetic talc are not available. However, the use for female hygiene of body powders, baby powders, talcum powders and deodorising powder, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries.³

From pathological studies it is known that particles and fibres that enter the body can migrate to distant organs. For instance, asbestos fibres have been found in ovaries from women exposed to asbestos.^{4,5} Analogously, following perineal application, talc particles can migrate from the vagina to the peritoneal cavity and ovaries.⁶ A majority of women experience retrograde menstruation⁷; this suggests a mechanism by which talc particles can travel through the female reproductive tract to the ovaries. Furthermore, epidemiological studies have shown decreased risks of ovarian cancer after tubal ligation and/or hysterectomy, suggesting that removing a pathway by which carcinogenic substances can reach the ovaries reduces the risk.^{8,9}

The association between talc use in the perineal region and ovarian cancer was investigated in one cohort study,¹⁰ and 20 case-control studies.^{11–30} In the cohort study, arguably the strongest study because of its partly prospective ascertainment of exposure, there was no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined. The various case-control studies provided indications of either a significant excess risk (10 studies) or non-significant excess risk or

null (10 studies), with odds ratios (ORs) ranging from 1.0 to 3.9. None of the studies reported relative risks below 1.0. The population-based case-control studies,^{11 15–17 20–26 28–30} included studies with 112–824 ovarian cancer cases, and had odds ratios ranging from 1.1 to 3.9 (fig 1). The hospital-based case control studies^{12–14 18 19 27} included studies with 77–462 cases, and reported odds ratios between 1.0 and 2.5. Pooled odds ratios were calculated by fixed effects model. As shown in figure 1 pooled ORs were 1.40, 1.12 and 1.35 for population-based, hospital-based and all case control studies combined, respectively. Some studies^{13 14 22 23 26 28} tried to assess exposure-response associations, in terms of frequency of use or length of use in years but found no clear trend.

Methodological factors such as recall bias should always be considered in case-control studies. It could have been a problem had there been widespread publicity about the possible association between use of body powder and cancer. The International Agency for Research on Cancer (IARC) working group considers that there has not been widespread public concern about this issue and therefore considers it unlikely that such a bias could explain the consistent findings. Another source of recall bias could result from the fact that women with the cancer tend to remember or over-report their use of body powder. The influence of this type of recall bias cannot be ruled out.

Eight of the population-based case-control studies^{11 16 22–24 26 28 29} were identified, by the IARC working group as being most informative in terms of size of the studies, whether the studies were population-based, participation rates and adjustments of confounding variables. The selected studies included at least 188 cases and had participation rates ranging from 60% to 75%. Among these eight studies, the prevalence of perineal use of talc-based body powder among controls ranged from 16% to 52%. The relative risks of ovarian cancer among body powder users were homogeneous across this set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 12 case-control studies, most also reported relative risks of this magnitude or higher.

Information on talc use in infancy is generally insufficient in the case-control studies. However, in one study the exposure to baby powder was reported by 42.2% of the cases and 40.5% of the controls.¹⁵ In several of the other studies patients were asked about age at first use of perineal talc, as an indicator for use in infancy or other periods of life.

Only four case-control studies^{16 23 29 30} and one cohort study¹⁰ provided results by histological type. In four of these studies, in particular the cohort study, there were hints of higher risks of serous tumours related to talc exposure.

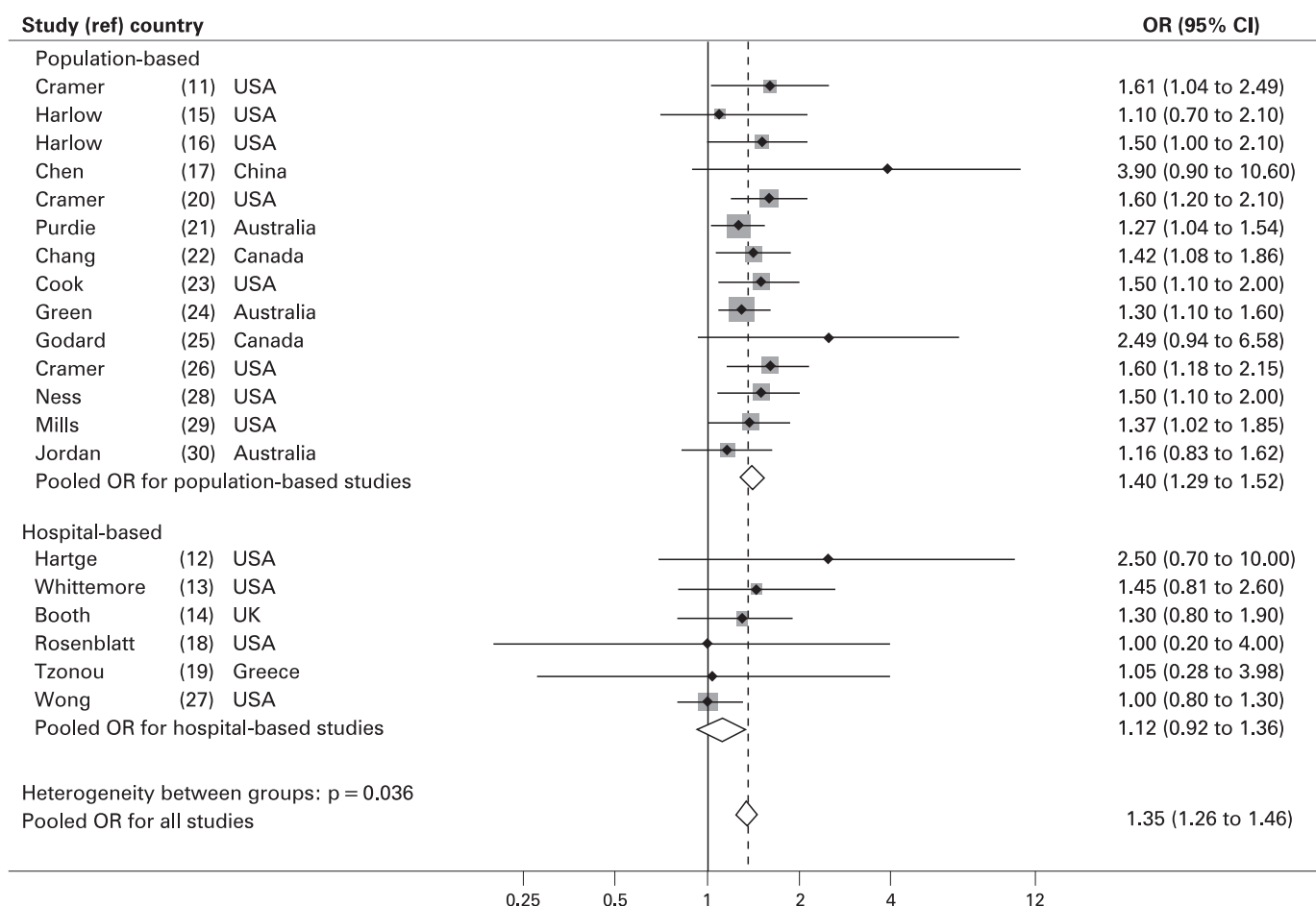


Figure 1 Results from case-control studies contributing data on perineal talc use and ovarian cancer. Results are presented as odds ratios (ORs) and their corresponding confidence intervals (95% CIs) and represented by squares and lines, respectively. Results are separated in 14 population-based and six hospital-based case-control studies. Pooled ORs for all population-based studies combined and all hospital-based studies combined are given. OR pooling by fixed effect models (Mantel-Haenszel method).

Before 1976, talc was to some extent contaminated with asbestos, so that the early studies relating talc to ovarian cancer may have been confounded by the asbestos.³¹ However, the association between talc exposure and ovarian cancer is as strong in recent studies,^{28–29} as in earlier ones, diminishing the likelihood that all these results are influenced by contamination of talc by asbestos.

To summarise the evidence in favour of an association, a very large number of studies have found that women who used talc experienced excess risks of ovarian cancer; some results were statistically significant and some were not. There was some indication in the cohort study of an increase in serous tumours. The evidence of talc migrating to the ovaries lends credibility to such a possible association. The main epidemiological evidence against the association is the absence of clear exposure-response associations in most studies, as well as the absence of an overall excess risk in the cohort study.

On balance, the epidemiological evidence suggests that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. The mechanism of carcinogenicity may be related to inflammation.³²

The carcinogenicity of non-asbestiform talc was assessed by a monograph working group at IARC in 2006.³³ After considering biases and possible confounding factors, the IARC working group concluded that the epidemiological studies provided

limited evidence for the carcinogenicity of perineal use of talc-based body powder, and classified this use as possibly carcinogenic to human beings (that is, group 2B).³⁴

PROPOSAL: TO RESEARCH COMMUNITY

The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk. Experimental research is needed to better characterise deposition, retention and clearance of talc to evaluate the ovarian carcinogenicity of talc.

The majority of the epidemiological studies carried out so far have been among American women. It would be instructive to seek evidence in other countries where perineal use of talc has been common.

While there has been some efforts to measure the degree of use, these have mainly been measured simply as the reported years of use. It is possible that the ostensible lack of exposure response trends is the result of crudeness of the exposure metric used. Therefore, it is important that future studies, irrespective of study design, devote some effort to better assessment of exposure. The use of body powders should be assessed both in terms of calendar time and age of the subject. Subjects should be asked about lifetime use, including age at initial use (infancy, childhood, teenager years, adulthood), age at which they stopped using such powders, gaps in the lifetime period of use

What this study adds

- Epidemiological evidence suggests that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. The IARC has classified this use of talc as possibly carcinogenic to human beings (group 2B).
- The mechanism of carcinogenicity may be related to inflammation. This paper focus on the high degree of consistency in the studies accomplished so far, and what should be the focus in future studies.

and frequency and nature of use (daily, during certain seasons of the year, only while menstruating). Another important question is whether the use of body powder was before or after tubal ligation or hysterectomy.

Individuals' answers to questions about use of brand names over time may be unreliable, and therefore, in future studies, investigators should try to ascertain, either from government or industry sources, the composition of the powders used in different time periods by different brand names and, in particular, to ascertain whether the exposure may have included some contamination by asbestos and also whether the exposure was to talc or a non-talc product. Statistical analyses should attempt to assess risk separately for the categories of powders: talc containing asbestos, talc not containing asbestos, non-talc product. Further, exposure metrics should take into account the age, duration and intensity of exposure. As well as analyses for all ovarian tumours combined, there should, if possible, be analyses by histological subtype and by invasiveness of the tumour.

While it would not be reasonable to envisage establishing a costly long-term prospective cohort study just to study this association, any long-term cohort study that is being set up to study cancer among women should collect information about talc use if the study is being conducted in a country where such use has been widespread.

In summary, future studies should focus on seeking evidence in talc-exposed female populations worldwide, collecting reliable information on age at initial use of body powder, exposure assessments and dose response associations.

Acknowledgements: The work reported in this paper was initiated while SH, JS and EW were part of an IARC Monographs Working Group of the International Agency for Research on Cancer, Lyon, France.

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Competing interests: None.

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Exhibit 6

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

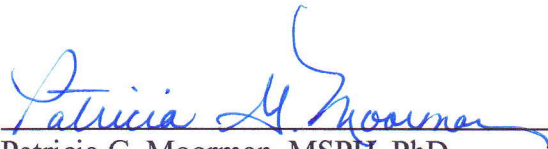
IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

RULE 26 EXPERT REPORT OF
PATRICIA G. MOORMAN, MSPH, PHD

Date: November 16, 2018


Patricia G. Moorman, MSPH, PhD

Scientific Review of the Epidemiologic Evidence on Talc Use and Ovarian Cancer

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Professor, Department of Community and Family Medicine
Cancer Control and Population Sciences, Duke Cancer Institute
Duke University School of Medicine
Durham, NC

Table of Contents

Background and Qualifications of Patricia G. Moorman, MSPH, PhD	3
Education	3
Professional Experience	3
Compensation and Testimony	4
Research Interests and Experience	4
Purpose	7
Role and Importance of Epidemiologic Studies	7
Methodology	9
Epidemiologic Studies Reviewed	11
Strength and Consistency of the Association	11
Temporality	29
Biological Gradient	29
Biologic Plausibility	32
Specificity	37
Coherence	37
Experiment	38
Analogy	38
Conclusion	38
References	41
Additional Materials and Data Considered	50

Background and Qualifications of Patricia G. Moorman, MSPH, PhD

I am a tenured professor in the Department of Community and Family Medicine, Duke University School of Medicine, Durham, NC and a member of the Cancer Control and Population Sciences Program in the Duke Cancer Institute. I am an epidemiologist with more than 25 years of experience in conducting research on women's health issues including ovarian cancer, breast cancer and menopause. Attached as Exhibit A to this report is a current copy of my curriculum vitae.

Education

I received a Bachelor of Science degree with distinction in pharmacy from the University of Kansas in 1980. I pursued graduate studies in epidemiology in the School of Public Health at the University of North Carolina-Chapel Hill, earning a Master of Science in Public Health (MSPH) in 1989 and a Doctor of Philosophy (PhD) degree in 1993.

Professional Experience

I have held positions in academic institutions since I completed my PhD, beginning as a research assistant professor in the Department of Epidemiology at the University of North Carolina-Chapel Hill from 1994 through 1996. From 1997 to 2000, I was an associate research scientist in the Chronic Disease Epidemiology division of the Yale University School of Public Health. I came to Duke University School of Medicine as an assistant professor in 2000, progressing through the academic ranks from associate professor, associate professor with tenure to my current position as professor in Community and Family Medicine. I also serve as the director of the Clinical Research Unit for the Department of Community Medicine and am a member of the Senior Faculty Advisory Committee for the Office for Research Mentoring in the School of Medicine. In addition, I am an adjunct faculty member in the Department of Epidemiology at the University of North Carolina-Chapel Hill.

Compensation and Testimony

My hourly billing is \$400. I have given deposition testimony in one case (Gail Ingham, et al., v. Johnson & Johnson, et al., Case No. 1522-CC10417-01, Circuit Court of the City of St. Louis, Division 10) and have not testified at trial in the last four years.

Research Interests and Experience

My primary research interests are in the area of women's health issues, with a particular focus on studying racial differences in risk factors and outcomes. I have had funding from the National Institutes of Health (NIH) for more than 20 years, which has supported my research in ovarian cancer, breast cancer and ovarian function after hysterectomy. Three of the key studies in my research career are: 1) the African American Cancer Epidemiology Study (AACES), a multi-center, case-control study of ovarian cancer in African American women,¹ 2) the Carolina Breast Cancer Study, which is one of the largest studies focused on understanding racial differences in breast cancer risk and outcomes,² and 3) the Prospective Research on Ovarian Function (PROOF) Study, a cohort study designed to examine risk for ovarian failure after premenopausal hysterectomy.³

Each of these studies involved primary data collection, meaning that the investigative team designed the data collection procedures, developed the surveys, recruited study participants and obtained questionnaire data and biological specimens from the participating women. Each study has made unique contributions to the scientific literature.

AACES has enrolled more than four times as many African-American women with ovarian cancer than any other study and is providing the most comprehensive epidemiologic data on ovarian cancer risk factors in this population to date.⁴⁻⁶ The Carolina Breast Cancer Study likewise provided key data on risk factors in African American women and was the first study to describe the markedly higher prevalence of the poor-prognosis basal subtype of breast cancer in young African American women.⁷⁻¹¹ The PROOF study is the largest prospective study of ovarian function after pre-menopausal hysterectomy and demonstrated that women

undergoing hysterectomy with ovarian conservation were at significantly increased risk for earlier menopause as compared to women who did not have a hysterectomy.^{3,12}

Our study team published an analysis of talc exposure and ovarian cancer in 2016, using data from AACES.¹³ This peer-reviewed paper, published in *Cancer Epidemiology, Biomarkers and Prevention*, was the first epidemiologic study of talc use and ovarian cancer that was focused exclusively on African American women. Our analyses found both a high prevalence of talc use in this study population and a statistically significantly increased risk for ovarian cancer among talc users. This paper was published prior to my involvement in litigation related to talc and ovarian cancer.

I have also been a co-investigator on the North Carolina Ovarian Cancer Study, which was a precursor to the AACES study. Data from this study were included in Terry, et al.'s¹⁴ 2013 analysis of genital powder use and ovarian cancer that pooled from data from eight case-control studies. I am currently an investigator in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium. The OCWAA consortium, which was initiated in 2016, is a multi-center collaboration that aims to bring together data from case-control and cohort studies to evaluate similarities and differences between African American and white women in ovarian cancer risk factors and outcomes.

In addition to these studies, I am an investigator with the Evidence Synthesis Group in the Duke Clinical Research Institute, a team of researchers that conducts evidence reviews of the scientific literature. I have worked with this group on a number of systematic reviews and meta-analyses on women's health issues including an evaluation of the benefits and risks of oral contraceptive use for primary prevention of ovarian cancer¹⁵⁻¹⁷ funded by the Agency for Healthcare Research Quality, and an evaluation of the benefits and harms of breast cancer screening¹⁸ funded by the American Cancer Society to help inform their screening mammography recommendations.¹⁹

I am an author on more than 130 scientific publications, with more than 50 of them directly related to ovarian cancer. The ovarian cancer papers address a wide variety of risk factors including reproductive and hormonal factors, lifestyle characteristics, genetic factors, and talcum powder products. The main focus of the manuscripts on which I have been the lead

author has been ovarian cancer risk factors in African American women and the effects of reproductive characteristics, hormones and other medications on risk for ovarian cancer.^{5,17,20-}

²³ The papers have been published in some of the leading journals in the field of epidemiology, gynecology and cancer including the *American Journal of Epidemiology*, *Cancer Epidemiology Biomarkers and Prevention*, *Obstetrics & Gynecology* and *Journal of Clinical Oncology*.

My teaching experience includes courses in Cancer Epidemiology for graduate students in public health and Evidence-Based Medicine for physician assistant students. A primary emphasis of these courses has been for the students to gain an understanding of the advantages and disadvantages of different types of studies used in clinical and epidemiologic research. In particular, the Evidence-Based Medicine course is designed to help the students learn how to critically appraise the medical literature and apply findings to clinical practice. In addition, I have mentored at the individual level public health graduate students and medical students.

I serve as an editorial reviewer for numerous journals and have served as a peer reviewer of grant applications on several dozen study sections over that past twenty years. I have reviewed NIH grants for a variety of funding mechanisms ranging from small grants (R03) to large multi-project applications (SPORC grants and Program Projects). I also have served as both peer reviewer and study section chair for the Susan G. Komen for the Cure Foundation and the Department of Defense Ovarian Cancer and Breast Cancer Research Programs.

In summary, in a career spanning more than 25 years, I have devoted my efforts to understanding factors that affect risk for ovarian cancer, breast cancer and menopause. I have conducted original research, giving me a deep appreciation of the advantages and disadvantages of different study designs and the challenges of collecting high-quality data for making etiologic inferences. I also have conducted research involving synthesis of the published literature, with the goal of informing decisions based on the best available evidence. A large proportion of my publications have focused on the epidemiology of ovarian cancer, and many of the others focused on breast cancer or menopause have relevance to ovarian cancer because of shared risk factors for the conditions. Based on my education, experience, and expertise, I

am highly qualified to assess the literature on the use of talc in relation to ovarian cancer and provide an expert opinion to a reasonable degree of medical certainty.

Purpose

The purpose of this report is to summarize the epidemiologic evidence related to talc use and ovarian cancer risk and to make a judgment as to whether there is sufficient evidence, based on the totality of evidence from epidemiologic investigations as well as laboratory and mechanistic studies, to conclude with a reasonable degree of scientific certainty that talcum powder use is a causal factor for ovarian cancer.

Throughout the report, the term "talc" will be used to refer to talcum powder products, recognizing that commercial talc products can contain asbestos, talc containing asbestiform fibers (e.g., talc occurring in a fibrous habit), heavy metals such as nickel, chromium and cobalt and fragrances.

Role and Importance of Epidemiologic Studies

It is important to bear in mind that epidemiologic research on factors that are thought to increase risk for cancer in human populations will consist of observational rather than experimental studies. As with most other now-known carcinogens, including cigarette smoke, it is both ethically wrong and pragmatically impossible to conduct randomized controlled trials to investigate whether a given exposure increases risk for cancer in humans. The judgment as to whether talc causes ovarian cancer will be based on epidemiologic studies in which the investigators collected and analyzed information on exposures (i.e., talc use and other risk factors) that the study participants chose to use, rather than studies in which exposures were randomly assigned to the study subjects in an experimental setting.

Observational study designs used in the study of talc and ovarian cancer include cohort and case-control studies, both of which are well-established and generally accepted methods for studying cancer etiology. In a prospective cohort study, a large group of individuals (the cohort) is identified and exposure to various factors hypothesized to affect risk of disease is

assessed at the time of enrollment (baseline). The cohort is followed over time and the analyses focus on whether the exposed group is more or less likely to develop the outcome of interest than the unexposed group. Some of the prominent advantages of cohort studies are that multiple outcomes/diseases can be assessed within the cohort and exposure assessment precedes the development of the disease, limiting recall bias. However, a primary disadvantage of cohort studies, particularly in relation to cancer etiology studies, is that they must enroll tens of thousands of subjects and follow them for long periods of time to accrue enough cases to have a well-powered study. In addition, if cohort studies do not update exposure information after the baseline assessment, the exposure of some individuals in the cohort may be misclassified.

Case-control studies identify individuals with the disease of interest and an appropriate control group of individuals without the disease and assess exposures that are thought to increase or decrease the risk of the disease. The investigators then analyze whether cases are more likely than the controls to have a given exposure. Case-control studies focus on a single disease, therefore they typically collect more detailed risk factor information for that disease than cohort studies. A major advantage of case-control studies is that they are a more efficient design for studying diseases that are less common or have a long latency period. Therefore, they are very commonly used for etiologic studies of cancer. A disadvantage of case-control studies is that they collect exposure information for the cases after they have already been diagnosed with the disease, which raises concerns that cases may recall exposures differently from controls.

Cohort studies and case-control studies each have advantages and disadvantages for assessing talc as a risk factor for ovarian cancer, and one study design is not clearly superior to the other. In addition, specific details related to the conduct of the study such as methods of exposure assessment, length of follow-up and choice of control group can impact the validity of the findings and the interpretation of results. Therefore, rather than making a judgment based only on the overall study design, the evaluation and interpretation of the findings of the studies must consider the strengths and weaknesses of the individual studies. As the results of the

studies are described and evaluated in this report, specific advantages and disadvantages of individual studies will be discussed in more detail.

In contrast to studies on laboratory animals, studies on humans are subject to more variation in exposure assessment and it is impossible to control all other factors that may contribute to disease risk. For these reasons, judgments on causality from epidemiologic research typically are not based on a single study or even a few studies, but are based on the totality of evidence from multiple studies conducted in different study populations, in different locations and across different time periods. Evidence from the epidemiologic investigations is combined with relevant studies from other disciplines, including pathology, animal and mechanistic studies, to make an assessment of the evidence for a causal association between genital exposure to talcum powder and ovarian cancer.

Methodology

The methodology I used to assess the epidemiologic evidence on talc use as a causal risk factor for ovarian cancer involved conducting a literature search on PubMed using the terms “ovarian cancer” and “talc” to identify all relevant original studies, systematic reviews, meta-analyses, editorials and commentaries (search most recently updated on October 29, 2018). The search I did returned 131 articles, all of which were systematically considered and assessed as to their relevance to talc as a risk factor for ovarian cancer. Twenty-nine articles were not directly relevant to the question at hand (mostly addressing talc in the treatment of malignant pleural effusions). Of the remaining 101 articles, 36 were reports of original epidemiologic studies directly addressing genital talc exposure and ovarian cancer or meta-analyses of such studies.^{14,24-56} Other articles retrieved included studies of occupational talc exposure,⁵⁷⁻⁶² other original research articles that were not specifically epidemiologic studies of genital talc and ovarian cancer (e.g., studies of endometrial cancer, pathology studies, animal studies, etc.)⁶³⁻⁸⁰ and reviews, commentaries and letters^{60,81-120} I also examined reference lists from key articles to identify any additional relevant studies. In addition, I reviewed relevant studies as well as documents provided during the course of discovery process.

The primary focus of my review is the epidemiologic studies of genital talc exposure and ovarian cancer and the meta-analyses, with supporting information from other types of publications, including animal, pathology and mechanistic studies used as appropriate to address biological mechanisms underlying the association between talc use and ovarian cancer.

As I evaluated the individual epidemiologic studies (case-control and cohort studies) that described the risk for ovarian cancer associated with talc use, I did not weight one design more heavily than the other because there are advantages and disadvantages to each design for evaluating talc as a cause of ovarian cancer. I considered the potential biases of individual studies, both those that supported and those that did not support an association between talc and ovarian cancer, and how those biases may have impacted the findings. As I describe in this report, some biases have the potential to lead to an overestimate of the relative risk (e.g. recall bias in case-control studies) while others could result in an underestimate of the relative risk (e.g. incomplete ascertainment of talc use in the cohort studies).

I also considered the studies that combined data from multiple studies – meta-analyses or pooled analyses from multiple case-control studies. These types of analyses are often considered to be some of the strongest evidence for a causal association between an exposure and disease as they provide an estimate of the relative risk that is more statistically robust than individual studies. Data from meta-analyses are particularly important for evaluating exposure-disease relationships such as talc and ovarian cancer where the relative risks from most individual studies are approximately 1.2 to 1.5.

As is standard in epidemiologic research, my assessment of whether there is a causal association between talc use and ovarian cancer was guided by the aspects of a causal relationship described by Bradford Hill during the 1960's. Sir Austin Bradford Hill's writings on causal inference provide an accepted framework for assessing whether a given exposure is a cause of a specific outcome.¹²¹ The aspects of the associations that Hill described are: Strength, Consistency, Specificity, Temporality, Biological Gradient, Plausibility, Coherence, Experiment and Analogy. As his writings clearly state, these viewpoints or perspectives should be taken into account when assessing causality, but are not to be considered absolute criteria and not all must be checked off to make a conclusion of a causal relationship. Specifically, he states "What

I do not believe is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*.” This list of viewpoints was used to guide my assessment of the scientific literature on talc use and ovarian cancer.

It is important to point out that, in the end of this process, the assessment of whether a substance is or is not a causal risk factor for a given disease or condition involves scientific judgment that is made by considering and weighing the evidence. In any given case, it is not unusual for scientists and epidemiologists to weigh the Hill factors differently in reaching a conclusion on the causal inference in question. For example, scientists for many years debated the evidence that cigarette smoking causes lung cancer or asbestos causes lung disease.

Epidemiologic Studies Reviewed

Since 1982, when the first case-control study describing an increased risk for ovarian cancer associated with talc use was reported by Cramer, et al.,⁵⁰ more than two dozen additional reports of epidemiologic studies have been published.^{13,14,24-36,38-44,46-49,51-55,122,123} In some instances, data from a particular study were included in more than one publication, due either to an additional analysis of data from a cohort study with longer duration of follow-up (e.g.,^{31,34}) or to analyses that combined data from more than one study (e.g.,^{14,25}). Included in these publications are seven meta-analyses published between 1992 and 2018 that combined overall results from nine to 27 studies^{35,51,52,54-56} and a pooled analysis published in 2013 that combined individual level data from eight case-control studies.¹⁴

Strength and Consistency of the Association

The first two aspects of the causal relationship described by Bradford Hill, strength and consistency of association, are deeply intertwined. While Bradford Hill referenced the assumption that a larger relative risk is more likely to reflect a causal association, Hill also clearly stated that we should not be “too quick to dismiss a cause-and-effect hypothesis merely

on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so.”¹²¹

Seven meta-analyses of genital talc exposure and ovarian cancer^{35,44,51,52,54-56} calculated summary relative risks that were very consistent across the publications, ranging from 1.22 to 1.36, all with 95% confidence intervals excluding 1, indicating that women who reported talc use were at statistically significant increased risk for ovarian cancer. Similarly, the pooled analysis of eight case-control studies reported an overall odds ratio of 1.24 (95% confidence interval (CI) 1.15 – 1.33).¹⁴

To put this in context, it is useful to compare the epidemiologic data related to the strength of the association between genital talc use and ovarian cancer with some other well-accepted exposure-disease associations that have relative risks of similar magnitude and are generally accepted to be causal associations. Some examples of such associations and the relative risks from these exposures estimated from meta-analyses are:

1. Oral contraceptive use and breast cancer, relative risk 1.08 (95% CI 1.003-1.165) for ever versus never use and relative risk 1.21 (95% CI 1.04-1.41) for current or recent use versus never use¹⁶
2. Menopausal estrogen use and breast cancer, relative risk 1.20 (95% CI 1.06-1.37) for more than 5 years use versus no use¹²⁴
3. Passive smoking (also referred to as environmental tobacco exposure or secondhand smoke) and lung cancer, relative risk 1.27 (95% CI 1.17-1.37) for ever versus never exposure to a spouse who smoked¹²⁵
4. Residential radon exposure and lung cancer, relative risk 1.29 (95% CI 1.10-1.51) for highest versus lowest exposure¹²⁶
5. Trichloroethylene exposure and kidney cancer, relative risk 1.32 (95% CI 1.17-1.50) for occupational exposure.¹²⁷

Each of these exposure/disease associations is widely accepted as a causal relationship in the scientific community and has been judged to be a causal association by the International Agency for Research on Cancer (IARC).^{128-130 131} The estimates of the relative risks for these associations from meta-analyses or pooled analyses are approximately 1.25,^{16,124-126,132,133}

which is in the range of estimates of the relative risk from meta-analyses and pooled analyses for the association between genital talc use and ovarian cancer. Therefore, we have evidence of well-established causal associations in which the magnitude of the relative risk is very similar to what has been reported for genital talc use and ovarian cancer.

It is instructive to compare in more detail the epidemiologic data on passive smoke exposure to that of talc and ovarian cancer. Passive smoke exposure, like talc, is a very common exposure in the population that can only be assessed retrospectively through self-report, therefore it is difficult to determine the precise level of exposure. In a meta-analysis of 55 studies published between 1981 and 2006 that examined the risk for lung cancer in never smoking women with passive smoke exposure from their spouses, Taylor, et al.¹²⁵ reported a pooled relative risk of 1.27 (95% CI 1.17-1.37). The relative risks from individual studies ranged from 0.66 to 2.57, with 44 of the 55 (80%) individual studies reporting a relative risk or odds ratio >1. In the individual studies, only 10 of 55 (18%) reported statistically significant associations (2 of 7 cohort studies, 3 of 25 case-control studies with population-based controls and 5 of 23 case-control studies). These data show that among the many epidemiologic studies that assessed passive smoke exposure as a risk factor for lung cancer, not all had statistically significant findings and some even reported relative risks less than one, yet the overall conclusion from the totality of the evidence is that passive smoke exposure is causally associated with lung cancer.

The most recent meta-analysis published in 2018 on talc and ovarian cancer by Pennikilampi et al. reported a pooled relative risk of 1.31 (95% CI 1.24-1.39) with values from individual studies ranging from 0.73 to 3.90.⁵⁶ This result is consistent with other meta-analyses performed. Twenty-four of the 26 (92%) studies reported a relative risk or odds ratio >1, and statistically significant associations were reported in 14 of the 26 (54%) studies. This comparison illustrates that as compared to the well-established causal association between passive smoke exposure and lung cancer, the association between talc and ovarian cancer has a pooled relative risk estimate of similar magnitude with a greater proportion of the studies reporting relative risks >1 and a greater proportion reporting statistically significant

associations suggesting the evidence for talc and ovarian cancer is as significant as for passive smoke exposure and lung cancer.

These comparisons also illustrate the importance of meta-analyses in epidemiologic research when considering exposures for which the strength of association is approximately 1.5 or less. Individual studies, especially those with smaller samples sizes, may not detect a statistically significant increased risk. When the increased risks in this range are seen repeatedly, even when individual studies are not statistically significant, meta-analysis allows the data to be aggregated to make a conclusion that is more robust statistically. When combining these studies through meta-analysis, the totality of the data shows that there is indeed a statistically significant link between genital talc use and ovarian cancer. This observation has been quite consistent, with findings replicated in studies conducted by different teams of investigators, in different geographic locations within and outside the United States, in different race/ethnic groups and over a span of several decades.

In conjunction with the strength of the association, it is also critical to consider the prevalence of the exposure in the population when evaluating its public health impact. A risk factor that is less strongly associated with a disease but has a high prevalence in the population can be responsible for more cases of the disease than a risk factor that is more strongly associated with the disease but has a low prevalence in the population. A measure of the contribution of a risk factor to a disease is the population attributable fraction (PAF), which is defined as the proportion by which the incidence rates of the outcome in the population would be reduced if the exposure was eliminated.¹³⁴ Wu et al.²⁶ calculated the PAF for ovarian cancer related to talc exposure in their multi-ethnic case-control study in Los Angeles. The odds ratio for genital talc use was 1.46 (95% CI 1.27 – 1.69) and the prevalence of use was 41% among the cases and 31% among the controls. The PAFs for the different ethnic groups ranged from 12.2 to 15.1%, which is interpreted as the proportion of ovarian cancer cases that theoretically could be prevented if genital talc use in the population could be eliminated and there were no changes in other risk factors. In other words, of the estimated 22,440 cases of ovarian cancer diagnosed in 2017,¹³⁵ approximately 3,300 of them could theoretically have been prevented if women had not used genital talc. The PAF calculation demonstrates that even with an

estimated relative risk for genital talc use of less than 1.5, its high prevalence of use means that it contributes to a substantial proportion of the ovarian cancer cases in the population.

The overall associations seen in the talc-ovarian cancer meta-analyses as well as in many of the individual studies are statistically significant, indicating an increase in risk of approximately 25 to 30%. While not as high as other relationships like smoking and lung cancer, these relative risks are in line with other generally accepted causal relationships (e.g., second hand smoke and lung cancer). I consider the strength of the association seen in the talc-ovarian cancer epidemiologic studies, to be an important factor in favor of a causal relationship between talc and ovarian cancer, particularly when considered along with the consistency of the association seen across these studies.

As described above, among the more than two dozen studies that have reported on the association between talc use and ovarian cancer, the vast majority of them reported relative risks or odds ratios greater than one, indicating strong consistency in the direction of the effect. The findings from the multiple studies are summarized in seven meta-analyses published since 1992, including two published in 2017-18, that combined overall results from six to 27 studies assessing genital talc exposure and ovarian cancer^{35,51,52,54,55 56 44} and in a pooled analysis published in 2013 that combined individual level data from eight case-control studies.¹⁴ Of the 27 studies included in Berge et al.'s 2017 meta-analysis⁵¹, 24 were case-control studies (18 population-based,^{13,23,25,29,30,32,33,38,39,41,42,44,45,47,50,123,136,137} 5 hospital based,^{36,43,46,49,122} and 1 with both hospital and population controls⁴⁸) and three were prospective cohort studies^{24,27,31}. The calculated overall relative risks for all studies combined in these meta-analyses were 1.3 (95% CI 1.1 – 1.6),⁴⁴ 1.27 (95% CI 1.09-1.48),⁵⁵ 1.36 (95% CI 1.24-1.49),³⁵ 1.33 (95% CI 1.16-1.45),⁵⁴ 1.35 (95% CI 1.26 - 1.46),⁵² 1.22 (95% CI 1.13-1.30)⁵¹ and 1.31 (95% CI 1.24-1.39)⁵⁶ and 1.24 (95% CI 1.15-1.33) in the pooled analysis of eight case-control studies.¹⁴ The conclusions from these analyses were quite consistent, even with additional data accumulating over time, indicating that women who used talc products as compared to women who reported no talc use were at 22 to 36% increased risk for ovarian cancer.

When considering the consistency from a number of different studies and meta-analysis, an epidemiologist should evaluate potential sources of bias including but not limited

to publication bias, recall bias, selection bias and information bias. I discuss each of these below.

Publication Bias: When considering a body of epidemiologic evidence from multiple studies, several concerns arise about the completeness of the published data and whether there is selective publishing of studies that find significant positive associations. These concerns were addressed by two distinct analyses conducted in the most recent meta-analyses by Berge, et al. (2017) and Penninkilampi and Eslick (2018).^{51,56} The first approach reported was a funnel plot, which is a graphical technique that plots the relative risks derived from the studies on one axis and the standard error of the relative risk (an indicator of the size of the study) on the other. The concept driving this approach is that studies should cluster around the “true” relative risk in the population. Due to random statistical variation, some studies will have relative risks that are higher than the true relative risk and some will be lower than the true relative risk. As sample sizes increase, there should be more precise estimates of the relative risk, therefore larger studies would be expected to produce estimates closer to the true relative risk whereas smaller studies may produce results that deviate further from the relative risk in the overall population. When the study results are plotted, one would expect them to fall into a funnel shape, with the larger studies at the point of the funnel, clustered around the true relative risk in the population, and smaller studies, with more variation in results, showing greater deviation from the average, forming the wide part of the funnel. Notably, in these meta-analyses, the two studies with the highest relative risk estimates (Chen, et al.⁴⁵ with a relative risk of 3.90 and Godard, et al.³⁸ with a relative risk of 2.49) and the two studies with the lowest relative risks (Hartge, et al.⁴⁹ and Gonzalez, et al.²⁴) all had a modest number of cases (≤ 170).

A funnel plot provides a method for assessing publication bias, i.e., the bias that results from studies with statistically significant findings being more likely to be published than studies that show no association. If one is concerned that studies that showed no association between the exposure and outcome are less likely to be published, the funnel plot allows the visual assessment of this potential bias. A lack of symmetry in the funnel plot, with a deficit of studies showing no association between the exposure and outcome, would be an indication of

publication bias. The papers by Berge, et al.⁵¹ and Penninkilampi and Eslick⁵⁶ which are the only meta-analyses that specifically addressed publication bias, concluded that there was no serious publication bias based on both visual inspection of the funnel plot and a statistical assessment of the data from the funnel plot. Therefore, there is a high level of confidence that there has not been preferential publication of studies that found a positive association between talc and ovarian cancer.

A second approach used by Berge, et al.⁵¹ was a cumulative meta-analysis, in which they showed the estimated summary relative risks over time from the first published report in 1982 through the most recently published studies in 2016. The plot showed that after the first initial reports, the overall summary estimates stabilized with estimates in the range of 1.2 to 1.25 over the last 25 years even as more and more data accrued from additional published studies.

These quantitative analyses indicate that it is unlikely that there is publication bias in the talc and ovarian cancer literature (i.e., the analyses do not suggest that studies that found talc use to be a risk factor for ovarian cancer were more likely to be published than those that found no association). Furthermore, from a qualitative perspective, it is also unlikely that there is a substantial risk for publication bias. Given the considerable public health interest in the risk for ovarian cancer associated with a widely-used cosmetic product, it is probable that any well-designed and conducted study that addressed this question would be published, even if it had null findings. Notably, one of the most recent studies, the Sister Study,²⁴ was published even though it found no increased risk for ovarian cancer associated with talc use.

While the overall conclusions from the meta-analysis and pooled analyses are quite consistent, with an overall statistically significant estimate of the relative risk in the range of approximately 1.2 to 1.3, it is important to consider possible reasons for heterogeneity of the estimates between individual studies.

Among the individual studies that have examined the association between talc use and ovarian cancer, the majority have been case-control studies, with only three prospective cohort studies addressing this research question. The meta-analysis by Berge, et al.⁵¹ noted that the summary relative risk was driven by the stronger associations observed for case-control studies

(relative risk = 1.26 (95%CI 1.17 – 1.35) than for cohort studies (relative risk = 1.02 (95% CI 0.85 – 1.20), which leads one to try to understand possible reasons for the differences by study design and to consider the relative advantages and disadvantages of the different study designs, specifically in relation to the study of talc and ovarian cancer. While the cohort studies do not show a statistically significant association for ever use of talc and ovarian cancer overall, the recent meta-analysis by Penninkilampi and Eslick⁵⁶ reported a statistically significant association with the invasive serous subtype of ovarian cancer, which is both the most common subtype and the one with the worst prognosis.

Case-Control Studies – Strengths and Weaknesses: Case-control studies, which are very commonly used in cancer epidemiology, have particular advantages for studying a relatively uncommon cancer like ovarian cancer, which has an annual incidence (number of new cases) in the United States of approximately 11 cases per 100,000 women.¹³⁸ In this study design, women with ovarian cancer (the case group) are identified by the research team, typically through a cancer registry, shortly after receiving their diagnosis. A control group of women who do not have the disease are also identified and recruited for the study. Both the cases and the controls provide information on their past exposure history. In a typical case-control study, the study participants complete an extensive questionnaire focusing on a broad range of exposures that are hypothesized to either increase or decrease the risk for cancer. In regard to ovarian cancer, a typical questionnaire will include questions on demographic characteristics, reproductive characteristics like pregnancy and contraception, medical characteristics, family history of cancer and lifestyle characteristics such as dietary factors, smoking history, physical activity and talc use. Notably, some of the factors queried about are expected to increase risk (e.g., family history of ovarian or breast cancer, estrogen use during menopause, talc), whereas others are associated with reduced risk (e.g., oral contraceptive use, pregnancies).

One major advantage of a case-control study is that it is possible to identify and recruit a large number of cases within a relatively short timeframe. To illustrate this point, I will use the example of AACES, the case-control study that my colleagues and I initiated in 2010 to study ovarian cancer in African American women and which was the source of the data we used for our 2016 paper on talc and ovarian cancer.^{1,13} We have enrolled more than 600 women with

ovarian cancer and more than 700 control women over a period of approximately 6 years, making it by far the largest study of ovarian cancer in African American women. When the grant application was originally submitted to the National Cancer Institute, one reviewer expressed the opinion that a cohort study would be preferable to the case-control design we proposed. In our response to the review, we pointed out that a prospective cohort study was not feasible for studying ovarian cancer in this population if we hoped to obtain meaningful information in a reasonable timeframe. The Black Women's Health Study, a large prospective cohort study, enrolled approximately 60,000 women starting in 1995 with the goal of studying a wide variety of health outcomes in this population. (<https://www.bu.edu/bwhs/>) In regard to ovarian cancer, after 18 years of follow-up, only 115 cases of ovarian cancer had been diagnosed among women in the cohort.¹³⁹ Although a cohort of 60,000 women is a very large epidemiologic cohort, it is still inadequate to study a relatively uncommon disease like ovarian cancer in a time-efficient manner. We successfully made the argument to the reviewers that a case-control study was the only feasible way to investigate the etiology of ovarian cancer in a timely manner in the African American population. This example illustrates why it is to be expected that the majority of the epidemiologic studies of ovarian cancer would be case-control studies.

Although case-control studies are commonly used in epidemiologic studies of cancer, there are potential biases associated with this study design, including selection bias and recall bias. In this study design, the investigator must select a control group of individuals without the disease being studied as a comparison group to determine the relative frequency of the exposures in the case group as compared to the control group. The goal of selecting a control group is to identify a group that is representative of the population from which the cases arose. This is often stated in textbooks as if someone in the control group were to develop the disease being studied, s/he would have been selected as a case for the study. There are many possible strategies for identifying and recruiting population-based controls, including the use of town registry books,^{25,50} telephone recruitment through random digit dialing^{13,25,29}, neighborhood recruitment,³⁰ driver's license records²⁵ and electoral rolls.¹²³ In hospital-based case-control studies, controls are typically selected from other hospitalized patients, with different studies

applying different criteria for eligible diagnoses among the controls, including other cancer diagnoses or specific non-cancer diagnoses.^{36,43,46,49,122}

Among the studies included in the recent meta-analyses, six were hospital-based case-control studies.^{36,43,46,48,49,122} The individuals that comprised the control group varied between these studies including patients with non-gynecologic malignancies,³⁶ patients treated for conditions other than gynecologic or malignant diseases,¹²² patients treated for conditions other than those related to reproductive history or oral contraceptive use,⁴⁶ patients treated for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy,⁴⁹ both hospital patients and population-based controls⁴⁸ and hospital visitors.⁴³ While the use of hospital controls may be efficient, concerns are often raised as to whether the controls are representative of the population from which the cases arose in terms of the exposures they experienced or their underlying risk for cancer. This is a particular concern with the study by Wong, et al,³⁶ which is the largest of the hospital-based case-control studies and one that found no association between talc use and ovarian cancer (OR=0.92, 95% CI 0.24-3.62). The control group in this study was “female patients treated for non-gynecologic malignancies during the same period”. Standard epidemiologic textbooks (e.g., Rothman, *Modern Epidemiology*¹⁴⁰) state that controls should be selected from the same source population or study base that gives rise to the cases. It is difficult to make the argument that other cancer patients represent the source population from which the ovarian cancer cases arose, which suggests that this was a poor choice of a control group that could have led to biased findings.

Another of the hospital-based studies, the study by Tzonou et al.⁴³ which reported a relative risk of 1.05, also had a significant limitation. This study was conducted in Greece, and the overall prevalence of talc use in the study population was 3.5%. Given the small sample size and the low prevalence of exposure, this population was ill-suited to study the relation between talc use and ovarian cancer.

As noted in the meta-analysis by Penninkilampi and Eslick,⁵⁶ the hospital-based studies were older (published before 2000) and with the exception of the Wong study³⁶, all were smaller studies that included fewer than 200 cases. The summary odds ratios from the hospital-based studies was lower but not significantly different than the summary odds ratio from

population-based studies (OR 1.22 versus 1.33, respectively),⁵⁶ a result that is not surprising given the important limitations in some of the hospital-based studies.

While there is no ideal method for control selection, arguably population-based control recruitment is more likely to result in a control group that is representative of the population from which cases arose. All of the larger case-control studies that investigated talc use and ovarian cancer (i.e., those with more than 500 cases) were population-based,^{13,23,25,29,30,33,42,123,137} which should have minimized selection bias.

Recall Bias: Recall bias is another possible bias in case-control studies. Recall bias is defined as systematic error due to differences in accuracy or completeness of recall of prior events or experiences.¹³⁴ It is a concern with case-control studies because information on exposures is obtained through interviews or questionnaires completed after the cases have already been diagnosed with the disease. It is thought that people affected with a disease may have given more thought to possible causes of that disease and have more accurate recall of risk factors than a person serving as a control in the study.

A distinction is made between *recall bias*, which arises from cases recalling exposures differently than controls, and *inaccurate recall* of an exposure that is difficult to remember with precision. Recall bias, which is considered differential misclassification between cases and controls, can result in either an overestimate or underestimate of the true relative risk. Inaccurate recall that occurs to a similar degree in cases and controls is considered non-differential misclassification, and for a dichotomous outcome (e.g., ever vs. never use of talc) will typically result in an underestimate of the true relative risk. An exposure like talc use, especially when assessing use over many years, is clearly one that is subject to a certain amount of inaccurate recall. However, inaccurate recall alone would not result in the consistently increased relative risks observed in the vast majority of the case-control studies of talc use and ovarian cancer.

Therefore, recall bias, which theoretically could result in a biased estimate of the relative risk, must be considered. Situations where recall bias would be considered a particular threat to a study's validity would be: 1) the exposure of interest is one that could be considered sensitive (e.g., illicit drug use, induced abortions), 2) the study hypotheses are known to the

study subjects or interviewers, or 3) there has been considerable media attention focused on an exposure.

In regard to the first situation, genital talc use, while addressing a rather personal topic, would not be considered a particularly sensitive topic. One would not expect that women would be disinclined to report its use out of embarrassment or a desire to report what is perceived to be more socially acceptable as has been reported for exposures like induced abortion.¹⁴¹

As to the second point regarding the blinding of the interviewers and the study participants to the study hypotheses, this is standard practice in epidemiologic research. In addition, in the typical case-control study, the investigators are collecting a tremendous amount of questionnaire data to address numerous hypotheses and there is not a particular focus on a single exposure. As an example, the questionnaires from AACES and the North Carolina Ovarian Cancer study each took approximately 1 - 1.5 hours to administer and collected information on a large number of exposures including pregnancy history, contraceptive and hormone use, family history of cancer, medical history, psychosocial factors and lifestyle factors. Data were collected on factors that were expected to be associated with increased risk (e.g., family history of cancer, history of infertility, menopausal hormone use, talc use) as well as those expected to be associated with decreased risk (e.g., oral contraceptive use, pregnancies, physical activity). Given the broad range of hypotheses and the numerous exposures that the cases and controls were queried about and the fact that neither cases nor controls were told in advance of the interview about the specific topics that would be covered, it is unlikely that the women with ovarian cancer would have given more thought to their talc use resulting in substantial systematic over-reporting of talc use among cases. This is supported by studies of other cancers that used empirical data to assess the likely effect of recall bias on relative risk estimates when investigators examined numerous exposures and concluded that recall bias did not consistently lead to increased estimates of the relative risk.¹⁴²⁻¹⁴⁴

Further evidence that recall bias in case-control studies does not inevitably lead to an overestimate of the association between a risk factor and exposure comes from a recent review of meta-analyses of observational studies by Lanza et al.¹⁴⁵ This review analyzed a random

sample of 23 meta-analyses of observational studies addressing different exposure/disease associations published in 2013 and compared findings from case-control studies and cohort studies within individual meta-analyses to determine if conclusions from case-control studies were significantly different from those from cohort studies. The authors concluded that there was no significant difference in effect estimates between the case-control and cohort studies, suggesting that the study design did not have an important impact on the conclusions of the meta-analyses. Although recall bias *theoretically* could lead to an overestimate of the association between a risk factor and disease, the empirical evidence indicates that in practice the effect is small in most situations.

The third situation of the effect of media attention on an exposure deserves consideration as there has been reporting in the lay press in recent years about lawsuits involving talc and ovarian cancer. This concern is not relevant to the vast majority of the studies as virtually all of the data collection in the epidemiologic studies of talc and ovarian cancer occurred prior to such litigation. However one notable exception is AACES,¹³ which began enrollment in 2010 and included data collected up through August, 2015. At the recommendation of the reviewer who critiqued the manuscript when it was submitted for publication, our group examined the association between talc and ovarian cancer stratified by the date of enrollment. The odds ratio for genital talc use and ovarian cancer was 1.44 for the overall study population and 1.19 for the participants interviewed before 2014. These data do give some credence to the idea that recall bias could have led to the higher odds ratios when including women interviewed during the time when there was more media attention focused on this exposure, however the fact that the association was attenuated but not eliminated when considering the full study population suggests that the association is not due entirely to recall bias.

Another way to approach the issue of whether recall bias is a likely explanation for the association between talc use and ovarian cancer is to consider whether the association was observed for other gynecologic cancers. The data are admittedly very sparse in this regard, however the only published case-control study of talc use and endometrial cancer reported an odds ratio of 0.88 (95% CI 0.68 – 1.14).⁶⁷ A study of ovarian cancer that was conducted by

several of the same investigators as the endometrial cancer study used similar methodology, was conducted in a similar timeframe (early to mid-2000s) in the same geographic region (Australia) and reported a similar prevalence of talc use in the study population. In contrast to their endometrial cancer study in which the investigators observed a non-significant inverse association with talc use, the investigators found a statistically significant increased risk for ovarian cancer associated with talc use (odds ratio=1.17, 95% CI 1.01 – 1.36).¹²³ While this comparison clearly needs to be interpreted cautiously because there is only a single published case-control study of talc use and endometrial cancer, it does provide evidence to suggest that the association between talc and ovarian cancer observed in most case-control studies is not due simply to recall bias.

Cohort Studies – Strengths and Weaknesses: In contrast to the case-control study, the prospective cohort study design is less susceptible to the selection bias and recall bias described above. Women who develop cancer and the comparison group are from the same population (the cohort) so the bias that could arise from improperly selecting a control group is minimized. Similarly, because the exposure information is collected before the diagnosis of cancer, one would not expect that recall of exposures would differ between the women who went on to develop cancer and those who remained free of cancer.

Despite these advantages, cohort studies do have some important disadvantages in relation to studying cancer etiology. The first is that even with large cohorts, it takes many years for a reasonable number of cancers to develop within the cohort, especially for an uncommon cancer like ovarian cancer. When considering the statistical power of a study to assess the association between an exposure and a disease, the size of the cohort is not the only driver of study power. A more critical consideration is the number of cases that develop within the cohort, which in turn is dependent on the length of follow-up of the larger cohort. Therefore, a large cohort with a relatively short duration of follow-up during which time a small number of cases developed among cohort will have low statistical power. In contrast, the total sample size of a case-control study is likely to be much smaller than a cohort study, but if it has a larger number of cases, it will have greater statistical power than the cohort study.

Among the three cohort studies included in the most recent meta-analysis,⁵⁶ the Nurses' Health Study reported 307 cases in a cohort of 78,630 women after approximately 14 years of follow-up,^{34,146} the Women's Health Initiative reported 429 cases in a cohort of 61,576 women after a mean of 12.4 years of follow-up²⁷ and the Sister Study reported 154 cases in a cohort of 41,654 women after a mean of 6.6 years of follow-up.²⁴ Even with tens of thousands of women in these studies, the number of ovarian cancer cases within each cohort is smaller than the number of ovarian cancer cases in many of the case-control studies. In particular, the number of cases within the Sister Study is smaller than the number of cases in any of the case-control studies published since 1993. As described in a commentary by Narod⁸¹, the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2.

Another limitation of cohort studies that is of greater relevance to the question of talc use and ovarian cancer is information bias related to exposure assessment. Cohort studies are typically designed to examine many different outcomes that develop within the study population over time. The Nurses' Health Study (<http://www.nurseshealthstudy.org/selected-publications>) and Women's Health Initiative (<https://www.nhlbi.nih.gov/whi/references.htm>) have reported on many different outcomes including, but not limited to, multiple types of cancer, cardiovascular diseases, fractures, gastrointestinal conditions and mental health. In contrast, case-control studies focus on a single disease, such as ovarian cancer. Because cohort studies are designed to examine diverse outcomes, the questionnaires must obtain data on risk factors that are relevant to a wider variety of diseases. To keep the questionnaire to a manageable length, a cohort study will typically query about more risk factors but in less detail than a case-control study that is focused on a single disease. This is the case with the talc questions, with the cohort studies collecting less detailed information on talc use, especially in regard to duration and frequency of use, than most of the case-control studies.

It is also worth noting that cohort studies are also subject to recall errors, especially when assessing exposures that began early in life. When the cohort studies assessed talc use, they were asking women to recall their past use of the products up to the point of interview,

similar to how exposure is assessed in the case-control studies. In the Nurses' Health Study, the cohort members were aged 36 to 61 at the time talc use was assessed in 1982, and in the Women's Health Initiative, the mean age at enrollment was 63. Because many women initiate use of talc at a young age, the study participants would have been recalling exposures over several decades, and it stands to reason that there would be some errors in recall. Therefore, in cohort studies as in case-control studies, reported talc use was subject to some degree of inaccurate recall. This likely resulted in non-differential misclassification of the exposure, which usually results in an underestimate of the true relative risk.

Another concern with exposure assessment in cohort studies that is highly relevant to the question of talc use in relation to ovarian cancer is that risk factor information can change over time. If the questionnaire data that were collected when the cohort was assembled do not include a comprehensive exposure history to that time point and are not updated over time, the information may not reflect the complete exposure history of an individual in the time before she was diagnosed with cancer. This could result in some talc users being incorrectly identified as non-users or in incorrect estimates of the duration of exposure.

Incomplete exposure assessment is a potential problem for each of the three cohort studies that have reported on talc use and ovarian cancer, however it is a particular issue for the Sister Study²⁴ which reported a non-significant inverse association between talc use and ovarian cancer (relative risk of 0.73, 95% CI 0.44 – 1.20). Each of the cohort studies assessed talc use at a single point in time and did not update the information at subsequent follow-up interviews. The Nurses' Health Study collected limited information on talc exposure in 1982, and did not collect additional data on talc use in subsequent questionnaires between 1982 and when the results were described in papers published in 2000³⁴ and 2010.¹⁴⁶ Similarly, the Women's Health Initiative collected information on talc exposure when the women were enrolled into the study and did not obtain updated information during the years the cohort was followed. Therefore, any use of talc after that single exposure assessment was not captured, and there would be a certain amount of misclassification of the exposure in both the women who subsequently developed ovarian cancer and those who did not. If the misclassification was non-differential, meaning that the degree of misclassification was similar between the women

who developed ovarian cancer and those who did not, the predicted effect would be a bias towards the null.¹⁴⁰ In other words, non-differential misclassification of talc exposure (as a dichotomous variable) would mean that the observed relative risk was not as strong as it would have been if there had been not misclassification.

The degree of misclassification of exposure in the Sister Study²⁴ is apparently much greater than in the other cohort studies. Use of talc was assessed through questions about personal care products used only in the 12 months prior to enrollment, including genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap or vaginal area. This assessment is essentially a “snapshot” of talc use during a short period of time, capturing neither the cumulative use of talc up to that point nor any subsequent use of talc after the baseline interview. Not surprisingly, the reported prevalence of talc use was quite low in this study. The 14% prevalence reported in the Sister Study was markedly lower than the other two cohort studies (40.2% in the Nurses’ Health Study³⁴ and 52.6% in the Women’s Health Initiative²⁷) as well as in nearly all of the case-control studies. In addition to underestimating the prevalence of talc use in their population, their assessment of talc only during the year prior to enrollment probably did not capture exposure during the most relevant period of the woman’s life. As the authors acknowledged in their paper, if latency (the time between exposure and diagnosis of cancer) is 15 to 20 years, the exposure assessments do not accurately reflect the period of risk. The limitations in the assessment of talc use raise serious questions about the validity of the findings from the Sister Study for this particular exposure. It is impossible to predict the direction or the magnitude of the association between talc use and ovarian cancer if the Sister Study had conducted a more complete assessment of the exposure.

A further limitation of the exposure assessment in the Nurses’ Health Study and Women’s Health Initiative is that neither assessed both the frequency and duration of use of talc. This additional limitation has ramifications for assessing dose-response gradients, which will be discussed in a later section of this report.

While cohort studies are often considered a stronger study design for assessing causal relationships between an exposure and outcome, this is not absolutely true for all exposures and outcomes. Rather than making a judgement about the quality of evidence based solely on

study design, it is important to consider study design from a more nuanced perspective and consider whether a cohort or case-control study provides the most optimal assessment of the exposure and outcome. As described above, each of the three cohort studies that has addressed talc use and ovarian cancer risk had substantial limitations in their assessment of talc use within their study population, which weakens their conclusions that talc use is not significantly associated with ovarian cancer risk.

In addition, the Sister Study,²⁴ which is a study that was designed primarily to examine breast cancer outcomes among women who had a sister with breast cancer, the small number of ovarian cancer cases despite the large size of the cohort and the inadequate assessment of talc exposure arguably make it a much weaker study than some of the larger, well-designed population-based, case-control studies. Notably, this study, with a relative risk estimate of 0.73 (95% CI 0.44 – 1.20)²⁴ could be considered an outlier as it is only one of two studies that reported a relative risk substantially less than 1, the other being Hartge's 1983 hospital-based case-control study.⁴⁹

Uncontrolled Confounding in Observational Studies: Uncontrolled confounding is a potential concern in both case-control and cohort studies since they are observational studies. If a factor is associated with talc use *and* is a risk factor for ovarian cancer and is not accounted for in the statistical analysis, it could confound the association between talc use and ovarian cancer. In other words, if there is confounding, the increased risk observed with talc use could be due to the failure to account for the other risk factor. Vaginal douching, which was found to be associated with ovarian cancer risk in the Sister Study, was examined as a potential confounder of the association between talc use and ovarian cancer.²⁴ Their analyses showed that adjusting for douching using statistical modelling had a negligible effect on the association between talc use and ovarian cancer, providing no evidence of confounding. Other studies have either found an association between talc and ovarian cancer when controlling for douching⁴⁴ or found no association between douching and ovarian cancer,⁴⁹ thus the available data do not support that douching is a confounder of the association between talc and ovarian cancer. Although uncontrolled confounding is a theoretical possibility, to my knowledge, in the more

than 30 years of research on talc and ovarian cancer no such confounder has been identified that could account for the increased risk associated with talc use.

Overall, the meta-analyses indicate a high level of consistency in findings, especially from the case-control studies. Although weaker associations were observed in the cohort studies, the most recent meta-analysis did report statistically significant associations with invasive serous ovarian cancer in the cohort studies as well as in the case-control studies that reported on histologic subtype.⁵⁶ As a whole, the weaker associations observed for the cohort studies could be plausibly explained by limited methods used for talc exposure assessment, the limitations described above, including the most recent cohort study by Gonzalez, et al.,²⁴ which will have the predicted effect of biasing the results towards the null (i.e., showing an effect that is weaker than the true effect).

Taken as a whole, the overwhelming statistical strength of these studies, whose results are replicated over decades across a wide variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference.

Temporality

Temporality is the only consideration that is an absolute criterion when making a judgment of causality. This criterion states that a cause (the exposure) must precede the effect (the outcome of interest) in time. Both the cohort and case-control studies that examined talc use in relation to ovarian cancer assessed talc exposure that preceded the diagnosis. In cohort studies, the questionnaire data are obtained before any women in the cohort have a diagnosis of ovarian cancer, and in the case-control studies, women with ovarian cancer are asked to report on exposures that occurred before their diagnosis and controls are asked to report on exposures that occurred in a similar time frame. Therefore, there is no question that the exposure assessment captured talc exposure that preceded the diagnosis of ovarian cancer. Nevertheless, this factor is not highly weighted; while its absence would be fatal to a causal inference, its presence is not particularly compelling support for causation.

Biological Gradient

Associations that show evidence of a biological gradient, or dose-response relationship, are considered to have stronger evidence of causality. While the inconsistencies in reported dose-response trends for talc and ovarian cancer have been noted in some meta-analyses and reviews, e.g.,^{51,54} there are several considerations about this exposure that should be taken into account.

First, for an association like talc and ovarian cancer, the dose that is most relevant is the amount of talc that actually reaches the fallopian tubes and ovaries. The epidemiologic data rely on measures of external application as a surrogate of the level of exposure, not the actual exposure in the upper genital tract.

Second, there is some inherent inaccuracy in the measurement of the exposure, as the participants in most studies were asked to recall their duration and/or frequency of use over many years.

Third, the dose of talc exposure has been assessed differently across the studies. Some studies assessed only duration of use (months or years), some assessed only frequency of use (e.g., number of days per month) and some used measures of both duration and frequency to come up with a measure of total dose (estimated lifetime number of applications). The limitations of relying on duration or frequency alone as a measure of talc dose are apparent. For certain exposures, oral contraceptive use for example, duration of use is a good measure of total exposure because the pills are taken once daily. In contrast, patterns of talc exposure may be more inconsistent. Some women may use it daily, others only during their menstrual periods, others may apply it only during certain times of the year and others may have still different patterns of use. Measures of exposure based only on duration of use or only on frequency of use could result in inaccurate estimates of total exposure and obscure a dose-response relationship.

Some of the meta-analyses have cited the lack of a clear dose-response relationship as an argument against talc being a cause of ovarian cancer, and when considering measures of either years of talc use or number of applications of talc per month, there is considerable heterogeneity across studies. When considering the studies that examined dose-response associations considering both dose and frequency to estimate the total number of applications

of talc,^{13,14,25,29,30,32,35,41} the majority^{13,14,25,30,32} did find significant trends of higher risk with more lifetime applications of talc.

Terry, et al.¹⁴ noted in the pooled analysis of eight case-control studies that the trend for increasing risk for non-mucinous ovarian cancers with an increasing number of genital powder applications was significant when non-users were included in the analysis, but the trend was not significant when the analysis was restricted to ever users. The authors therefore concluded that the significant trend was largely due to the comparison of women who had ever used talc versus those who had never used it, suggesting that the dose-response relationship was not a simple linear increase in risk with greater exposure to talc.

While there is evidence of a dose response relationship in the majority of the studies that considered both frequency and duration of use (i.e., total number of applications), these observations are less consistent than the overall association between talc and ovarian cancer. There are several possible reasons why not all studies observed dose-response relationships, even when an overall association was observed in the study. First, there is likely to be greater inaccuracy in the recall of duration of use as compared to ever/never use, which would tend to obscure a dose-response relationship. Second, when “ever-users” were stratified into duration of use categories, it often resulted in strata with small numbers of women, resulting in less stable relative risk estimates within the duration categories. Third, as noted by Terry, et al.¹⁴, the dose-response relationship may not be a simple linear trend. In many of the studies, even the women in the lowest exposed category had hundreds of episode of talc exposure. Because there could have been considerable exposure even among the women in the “low” exposure categories, greater exposure may not have resulted in substantially increased risk and thus a linear trend may not have been apparent.

Overall, biological gradient was given lesser weight in my assessment of the literature, based on: 1) some of the studies that assessed a dose-response relationship evaluated only duration or frequency of use and not total number of applications, 2) duration and frequency of use are subject to more misclassification than ever use of talc, 3) small sample sizes within strata lead to unstable estimates, and 4) there is the possibility of a non-linear dose-response relationship. Nonetheless, even with these limitations, there was still evidence of a dose-

response relationship in the majority of studies that evaluated it based on the total number of applications.

Biologic Plausibility

Biological plausibility refers to whether there is a reasonable biological mechanism through which the exposure could lead to the disease. Hill is quick to point out that biological plausibility depends on the current state of scientific knowledge. Specifically, Hill wrote “It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.” It is clear that from these statements that the consideration of biological plausibility does not require that there is a *proven* biological mechanism to make a judgment of causality between an exposure and disease. Therefore, for this Hill consideration, a scientist looks for biological evidence that might explain the associations that are observed in the epidemiologic studies. In other words, one has to see whether the observed association “makes sense” biologically. In this case, I have considered both clinical plausibility and biological plausibility. Both of these show that the association seen in the epidemiologic studies “makes sense.”

It is probably safe to say that our understanding of the complex biological processes that lead from exposure to disease is incomplete for all cancers. In some instances, the precise biological mechanisms by which an exposure leads to disease remain unclear and in others, some mechanisms are well-established but there is not a complete understanding of why some exposed individuals develop the disease and others do not. An example of the former is alcohol consumption as a cause of breast cancer. While alcohol is considered by IARC to be an established cause of breast cancer,¹²⁸ recent publications still describe the association as one in which the exact biological pathways are unclear, even though several possible mechanisms have been hypothesized (i.e., metabolism to acetaldehyde or effects on estrogen levels).^{147,148} An example of the latter is smoking and lung cancer. Mechanisms of carcinogenesis from constituents of tobacco smoke have been well-described,¹⁴⁹ however it remains unclear as to why some smokers are more susceptible to developing lung cancer. In short, it is important to

recognize that biological plausibility depends on the current state of knowledge and may evolve over time as new evidence emerges.

When considering the likelihood of talcum powder products causing ovarian cancer, there is robust data that leads to the conclusion that there are biologically plausible mechanisms by which this exposure could lead to ovarian cancer. Specifically, 1) talcum powder products can migrate from the perineum through the genital tract to the ovaries and fallopian tubes, 2) talcum powder products can become imbedded in the ovarian tissue; 3) talcum powder products can induce an inflammatory response, and 4) the inflammatory response can result in increased oxidative stress and expression of cytokines, mutagenesis, and cell proliferation.

Pathology studies have demonstrated that particles may ascend the female genital tract from the vagina to the fallopian tubes and ovaries,^{150,151} and talc particles have been identified in ovarian tissue.^{71,76,78,79} In fact, the FDA's 2014 response to the Citizen's Petition requesting a cancer warning label on cosmetic talc products states that "the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable".¹⁵² Therefore, it is highly plausible that application of talcum powder products to the genital area can result in exposure to the ovaries.

It is also plausible that inhalation of talc products could also be a route of exposure leading to cancer. Studies of asbestos exposure indicate that inhalation of asbestos fibers can result in exposures to the peritoneal tissue, through transport through the lymphatic system and/or blood.¹⁵³⁻¹⁵⁵ There is strong evidence that such exposure can result in cancer, most notably mesothelioma. Inhalation of talcum powder products could result in similar peritoneal exposure.

Given the evidence that external application of talcum powder products can reach the ovaries either through upward migration through the genital tract or through inhalation and subsequent transport through the lymphatic system and/or blood, there are plausible biological pathways by which talc could lead to the development of ovarian cancer.

It is well-established through several lines of evidence that talc can cause inflammation. The inflammatory properties of talc are exploited for clinical use in talc pleurodesis, a treatment

for malignant pleural effusions or pneumothorax that involves instillation of talc into the pleural space.^(<https://www.uptodate.com/contents/talc-pleurodesis>) The resultant inflammation and fibrosis result in adhesion of the layers of the pleura, closing the pleural space. The inflammatory properties of talc are also evident in that chronic or acute exposure to talc through inhalation which can result in pulmonary talcosis, a chronic inflammation of the lower respiratory tract.^{156,157} Animal studies also confirm that talc causes inflammation, as experiments in rats treated with intra-vaginal or perineal talc showed inflammatory changes in the genital tract.⁷⁰ Although neoplastic changes were not observed in this experiment, this could be explained by the small number of animals (n=7) in each group or the duration of the experiment (3 months).

Inflammation has been identified as one of the hallmarks of cancer, with both extrinsic and intrinsic pathways described.^{158,159} Talc would be characterized as being involved in an extrinsic pathway, in which an exposure or condition results in chronic, non-resolving inflammatory responses. Chronic inflammation can lead to a cascade of cellular events that could result in damage to DNA, increased cell division and generation of inflammatory mediators.

Recent work by Saed, Fletcher, et al.^{160,161} describes the role of oxidative stress in the pathogenesis of ovarian cancer and the effects of talc on the oxidative state of ovarian cancer cell lines. Oxidative stress results when the balance between oxidant and anti-oxidant enzymes and molecules in cells is altered, resulting in an excess of reactive oxygen species or reactive nitrogen species. Oxidative stress, which can result from numerous factors including exposure to carcinogens, infection and chronic inflammation, has been shown to affect the initiation, promotion and progression of several types of cancer. Saed, et al. have reported that talc can generate a pro-oxidant state in both normal ovarian epithelial cells and ovarian cancer cells. Exposure to talc resulted in an increase in mRNA levels of certain pro-oxidant enzymes and a decrease in the mRNA of several anti-oxidant enzymes, suggesting a possible cellular mechanism by which exposure to talc could contribute to the development of ovarian cancer.

There is also evidence in the medical literature that talc products contain additional constituents that are known ovarian carcinogens, particularly asbestos.¹⁶²⁻¹⁶⁶

Asbestos is one of the most established carcinogens in our environment, and is associated with a variety of cancers including mesothelioma, lung, larynx and ovarian.^{167,168} IARC has stated that “a causal association between exposure to asbestos and cancer of the ovary was clearly established,” based on strongly positive cohort mortality studies of women with occupational exposure to asbestos as well as studies of women with environmental exposure to asbestos.¹⁶⁹ The Occupational Safety and Health Administration has stated that “there is no safe level of asbestos exposure for any type of asbestos fiber” and that asbestos exposures as short as a few days have resulted in cancer (mesothelioma), indicating that even low levels of exposure may be carcinogenic. (<https://www.osha.gov/SLTC/asbestos/>)

Although it has been often stated that talc products manufactured after 1976 are asbestos-free, evidence from published scientific reports,^{57,162} analyses performed on samples manufactured and packaged at different time points after 1976,¹⁷⁰⁻¹⁷³ and internal documents and testimony from the defendants demonstrate that statement is inaccurate.^{174,175} There is evidence that products manufactured after 1976 are not asbestos-free. Studies from Longo, et al. show that talc products can contain asbestos and talc containing asbestiform fibers (e.g., talc occurring in a fibrous habit).^{170,171} Therefore it is reasonable to conclude that women who regularly used talc products, both before and after 1976, were likely exposed to asbestos and talc containing asbestiform fibers through their use of these products.

Analyses of talcum powder products also demonstrate the presence of other constituents such as chromium and nickel which are well established carcinogens, and cobalt which is considered a possible carcinogen.^{169,174} I have also reviewed a report analyzing the 150+ known fragrance ingredients in talcum powder products, many of which have been determined harmful to humans.¹⁷⁶ The presence of these substances provide further evidence that exposure to talc products could result in cancer

It is also plausible that even among women recently diagnosed with ovarian cancer, exposure to the pre-1976 talc products, which are generally understood to have contained asbestos and talc containing asbestiform fibers, increased their risk for ovarian cancer. It is well-established that many cancer risk factors have a long latency, which the National Cancer Institute defines as “the time that passes between being exposed to something that can cause

disease and having symptoms”. Numerous examples of cancer risk factors with prolonged latency periods exist. For example, lung cancer typically is not diagnosed among cigarette smokers for several decades after initial exposure¹⁷⁷ and having severe sunburns during childhood is a risk factor for melanoma,¹⁷⁸ which has a median age of diagnosis of 63 years.¹³⁵

It has also been reported that the latency period between exposure to asbestos and mesothelioma (the cancer most strongly linked to asbestos exposure), ranges from 15 to more than 70 years.^{179,180} The median latency has been estimated at 22 to 32 years, with longer latency periods estimated for women than for men.^{179,180} Thus, it is not unreasonable to conclude that exposure to talc products early in a woman’s life could result in ovarian cancer decades later.

Further, other established risk factors for ovarian cancer also demonstrate long latency periods. Oral contraceptive use and history of pregnancy are two of the factors that are most consistently reported in association with ovarian cancer (both of which reduce risk). Although, these are “exposures” that typically occur when women are in their teens, twenties or thirties, the median age of diagnosis of ovarian cancer is 61 years, suggesting that events and exposures from early in a woman’s reproductive life can influence her risk for ovarian cancer decades later.

The totality of this evidence indicates that there are plausible biological pathways by which use of talc products could lead to ovarian cancer. There is clear evidence that external applications of these products can result in exposure to the ovaries, through upward migration through the genital tract or inhalation exposure. Once exposed, there are plausible biological mechanisms, by which talc itself or constituents of the talcum powder product could lead to carcinogenic transformation of ovarian cells. This includes credible evidence that talc products contain asbestos fibers, a known ovarian carcinogen, regardless of whether they were manufactured before or after 1976. While it is likely that advances in scientific knowledge may further refine our understanding of how talc exposure can lead to ovarian cancer, our current knowledge is adequate to conclude that there are plausible biological pathways leading from talc exposure to ovarian cancer.

I have considered the biologic plausibility that would support and detract from the hypothesis that talcum powder products can cause ovarian cancer. The more persuasive evidence is that talc can migrate to the ovaries through the genital tract and become imbedded in ovarian tissue. It is also plausible that talc could reach the peritoneal cavity through an inhalation route. Regardless of the route of exposure, it is clear that talcum powder products, including constituents like asbestos and fibrous talc, may cause an inflammatory response and oxidative stress that could lead to cell damage. These biologically plausible mechanisms are a persuasive explanation for the consistent increased risk we have observed in the epidemiologic studies. *Simply put, the observed association “makes sense” biologically.* Along with consistency and strength, I considered this a strong factor favoring a causal inference.

Specificity

As described by Hill,¹²¹ if specificity exists between an exposure characteristic and disease, it provides strong evidence of causality. However, he also stated that “one-to-one relationships are not frequent ...multi-causation of disease is generally more likely than single causation”. Clearly, ovarian cancer has multiple causes, with talc exposure among many known risk factors. From the standpoint of there being a “one-to-one relationship” between talc and ovarian cancer, there is not a high level of specificity. However, given that talcum powder products are particularly associated with epithelial ovarian cancer, especially serous ovarian cancer, it does support that it is a fairly specific relationship. This aspect was given only modest weight, because talc is one of many possible causes of ovarian cancer.

Coherence

It is recognized that the plausibility depends on the current state of biological knowledge. Knowledge of the biological mechanisms for ovarian carcinogenesis (and virtually any other disease) is incomplete and will continue to evolve as further research continues. Coherence, as described by Hill, means that, even if the knowledge of biology of the disease is not well-defined, the “data should not seriously conflict with the generally known facts of the natural history and biology of the disease”.¹²¹ Given the current state of knowledge of ovarian

carcinogenesis, the postulated mechanisms by which talc exposure leads to ovarian cancer do not conflict with the current state of knowledge on ovarian carcinogenesis. This aspect was given considerable weight as it is important that the overall evidence fit together in a coherent manner. Taking into account the plausible pathways by which talc products could reach the target tissue, the expected latency period between exposure and disease, and biological mechanisms that are consistent with our knowledge of carcinogenesis, the data are consistent with the natural history and biology of ovarian cancer.

Experiment

As described above, the epidemiologic data on talc use and ovarian cancer are from observational studies, therefore there are no clear cut experimental data on which a causal assessment can be made. Hill acknowledged that experimental data are often not available for the exposure/disease associations under study, but in some circumstances, experimental or semi-experimental evidence is available.¹²¹ For example, if a preventive action is taken to remove the exposure and the incidence of disease declines, there is strong support for a causal relationship. No such experimental evidence is available for talc use and ovarian cancer.

Analogy

The final viewpoint defined by Hill ¹²¹ is analogy, whereby evidence of an association with one risk factor would suggest that a similar risk factor could also plausibly be associated with the disease. Because this viewpoint is rather vague, it is often not incorporated into causal assessments. Nevertheless, while I did not weight it heavily, the similarity between asbestos and asbestiform talc – both of which are widely accepted as causing ovarian cancer – is supportive of this viewpoint.

Conclusion

Epidemiologic evidence linking genital talc use to ovarian cancer has been accruing since 1982.⁵⁰ As I evaluated this evidence, I considered the results from individual studies with different designs (case-control and cohort) as well as meta-analyses and a pooled analysis of

multiple case-control studies. In my evaluation of the data, I considered the strengths and weaknesses of individual studies, recognizing that there are advantages and disadvantages of both case-control and cohort studies for evaluating talc as a risk factor for ovarian cancer. I used the Bradford Hill framework as a guide for making my weight of the evidence assessment of whether there is evidence for a causal association between talc use and ovarian cancer.

The epidemiologic evidence I evaluated was derived from more than two dozen studies conducted in many different settings. The vast majority of studies reported relative risks or odds ratios greater than one, indicating that women with ovarian cancer were more likely to have used talc products than women without ovarian cancer. Meta-analyses, which combine findings across multiple studies to come up with an overall estimate of risk that is more statistically robust, have consistently reported that there is a statistically significant increased risk for ovarian cancer among women who reported genital talc use. While meta-analyses have noted that the relative risk estimates from case-control studies have been larger than from cohort studies, limitations in all of the cohort studies could explain the weaker associations observed in these studies. It is also noteworthy that the most recent meta-analysis⁵⁶ reported significantly increased risks for invasive serous ovarian cancer, which is the most common subtype as well as the one with the worst prognosis, in both cohort and case-control studies.

The epidemiologic studies that have examined talc use in relation to ovarian cancer risk have been conducted in very diverse populations, both within and outside the United States and in women of different race/ethnicities. The consistency of the findings across populations adds credibility to the findings of increased risk of ovarian cancer among talc users.

The relative risk estimates in most studies and the summary relative risk estimates from the meta-analyses are of a magnitude (~1.25-1.30) that is comparable to other common exposures that are causally related to cancer (e.g., passive smoke exposure and lung cancer, oral contraceptive use and breast cancer, menopausal estrogen use and breast cancer, residential radon exposure and lung cancer). Additional evidence supportive of talc being an ovarian cancer risk factor are biologically plausible mechanisms based on inflammation pathways, oxidative stress and the presence of asbestos, asbestiform talc, and other known

carcinogens in talcum powder products. Evidence of a dose-response relationship exists in many of the studies that considered both duration and frequency of exposure.

Based on the evidence in total, it is my opinion with a reasonable degree of scientific certainty that use of talcum powder products can cause ovarian cancer. I reserve the right to modify or refine my opinions based on additional scientific evidence that may emerge on this topic.

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EXHIBIT A

***Duke University Medical Center
Curriculum Vitae***

Date Prepared: October 2018

Patricia Gripka Moorman, M.S.P.H., Ph.D.

Primary academic department: Department of Community and Family Medicine
Duke University Medical Center

Present academic rank and title: Professor with tenure, September 2014

**Date and rank of first Duke
faculty appointment:** July 1, 2000, Assistant Professor

Medical licensure: N/A

Date of birth: December 19, 1957

Place of birth: Kansas City, Kansas, USA

Citizen of: United States of America

EDUCATION

	Institution	Year	Degree
High School	Bishop Ward High School Kansas City, KS	1975	Diploma
College	University of Kansas Lawrence, KS	1980	B.S. with distinction, Pharmacy
Graduate School	University of North Carolina – Chapel Hill Chapel Hill, NC	1989	M.S.P.H., Epidemiology
	University of North Carolina – Chapel Hill Chapel Hill, NC	1993	Ph.D., Epidemiology

PROFESSIONAL TRAINING AND ACADEMIC CAREER

Institution	Position/Title	Dates
Shalinsky Drugs, Kansas City, KS	Pharmacist	1980-1981
Community Pharmacy, Wrentham, MA	Pharmacist, Manager	1981-1982
Revco Drugs, Durham/Raleigh, NC	Pharmacist, Manager	1983-1993
Department of Epidemiology University of North Carolina - Chapel Hill	Graduate Research Assistant Teaching Assistant	1987-1993
Burroughs Wellcome Research Triangle Park, NC	Epidemiology Research Associate Summer Intern	1988
Department of Epidemiology Lineberger Comprehensive Cancer Center University of North Carolina - Chapel Hill	Research Assistant Professor	1994-1996
Dept. of Epidemiology and Public Health Yale Comprehensive Cancer Center Yale University School of Medicine New Haven, CT	Associate Research Scientist	1997-2000
Department of Epidemiology University of North Carolina - Chapel Hill	Adjunct Assistant Professor Adjunct Associate Professor	2000-2005 2005-present
Dept. of Community and Family Medicine Duke University Medical Center	Assistant Professor Associate Professor (non-tenured) Associate Professor (tenured) Professor (tenured) Clinical Research Unit Director (formerly Site-Based Research Director)	2000-2004 2004-2008 2008-2014 2014-present 2009-present

PUBLICATIONS

Refereed Publications

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88. Hill DA, Horick NK, Isaacs C, Domchek SM, Tomlinson GE, Lowery JT, Kinney AY, Berg JS, Edwards KL, **Moorman PG**, Plon SE, Strong LC, Ziogas A, Griffin CA, Kasten CH, Finkelstein DM for the Cancer Genetics Network. Long-term risk of medical conditions associated with breast cancer treatment. *Breast Cancer Res Treat* 2014; 145: 233-43. (PMCID: PMC4096572)
89. Gaines AR, Turner EL, **Moorman PG**, Freedland SJ, Keto CJ, McPhail ME, Grant DJ, Vidal AC, Hoyo C. The association between race and prostate cancer risk on initial biopsy in an equal access, multiethnic cohort. *Cancer Causes Control* 2014; 25: 1029-35. (PMCID: PMC4117308)
90. Davidson BA, **Moorman PG**. Risk-benefit assessment of the combined oral contraceptive pill in women with a family history of cancer. *Expert Opinion Drug Safety* 2014; 10: 1375-82.
91. Allott EH, Tse CK, Olshan AF, Carey LA, **Moorman PG**, Troester MA. Non-steroidal anti-inflammatory drug use, hormone receptor status, and breast cancer-specific mortality in the Carolina Breast Cancer Study. *Breast Cancer Res Treat* 2014; 147: 415-21. (PMCID: PMC4462196)
92. Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Peters E, Schwartz AG, Terry P, Wallace K, Akushevich L, Wang F, Crankshaw S, **Moorman PG**. A Multi-Center Population-Based Case-Control Study of Ovarian Cancer in African-American Women: The African American Cancer Epidemiology Study (AACES). *BMC Cancer* 2014; 14: 688. (PMCID: PMC4182887)
93. Myers ER, **Moorman P**, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, Davidson B, Chatterjee Montgomery R, Crowley MJ, McCrory DC, Kendrick A, Sanders GD. Benefits and Harms of Breast Cancer Screening: A Systematic Review. *JAMA* 2015; 314: 1615-34.
94. Qin B, **Moorman PG**, Alberg AJ, Barnholtz-Sloan JS, Bondy M, Cote ML, Funkhouser E, Peters ES,

- Schwartz AG, Terry P, Schildkraut JM, Bandera EV. Dietary carbohydrate intake, glycemic load, glycemic index and ovarian cancer risk in African-American women. *Br J Nutr* 2016; 115: 694-702. (PMCID: PMC4844174)
95. Erondy CO, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Peters E, Schwartz AG, Terry PD, Wallace K, Akushevich L, Wang F, Crankshaw S, Berchuck A, Schildkraut JM, **Moorman PG**. The association between body mass index and presenting symptoms in African American women with ovarian cancer. *J Women's Health* 2016; 25: 571-8. (PMCID: 4900212)
96. Alberg AJ, **Moorman PG**, Crankshaw S, Wang F, Bandera EV, Barnholtz-Sloan J, Bondy M, Cartmell KB, Cote ML, Ford ME, Funkhouser E, Keleman L, Peters ES, Schwartz AG, Sterba KR, Terry P, Wallace K, Schildkraut JM. Socioeconomic status in relation to the risk of ovarian cancer in African American women: a population-based case-control study. *Am J Epidemiol* 2016; 184: 274-83. (PMCID: PMC4983652)
97. Peres L, Camacho F, Abbott S, Alberg A, Bandera E, Barnholtz-Sloan JS, Bondy M, Cote M, Crankshaw S, Funkhouser E, **Moorman P**, Peters E, Schwartz AG, Terry P, Wang F, Schildkraut J. Analgesic medication use and risk of epithelial ovarian cancer in African American women. *Br J Cancer* 2016; 114: 819-25.
98. Abbott SE, Bandera EV, Qin B, **Moorman PG**, Barnholtz-Sloan J, Schwartz AG, Funkhouser E, Peters ES, Cote ML, Alberg AJ, Terry P, Bondy M, Crankshaw S, Wang F, Camacho F, Schildkraut JM. Recreational physical activity and ovarian cancer risk in African American women. *Cancer Med* 2016; 5: 1319-27.(PMCID: PMC4924390)
99. Trabuco E, **Moorman PG**, Algeciras-Schimmich A, Weaver AL, Cliby W. Association of ovary-sparing hysterectomy with ovarian reserve. *Obstet Gynecol* 2016; 127: 819-27. (PMCID: PMC5004761)
100. Bandera EV, Qin B, **Moorman PG**, Alberg AJ, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Peters ES, Schwartz AG, Terry P, Schildkraut JM. Obesity, weight gain, and ovarian cancer risk in African American women. *Int J Cancer* 2016; 139: 593-600. (PMCID: PMC4982766)
101. Schildkraut JM, Abbott SE, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote M, Funkhouser E, Peres LC, Peters ES, Schwartz AG, Terry P, Crankshaw S, Camacho F, Wang F, **Moorman PG**. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev* 2016; 25: 1411-17. (PMCID: PMC5050086)
102. **Moorman PG**, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Peters ES, Schwartz AG, Terry P, Crankshaw S, Wang F, Schildkraut JM. Reproductive factors and ovarian cancer risk in African American Women. *Ann Epidemiol* 2016; 26: 654-62. (PMCID: PMC5035608)
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104. Peres LC, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, **Moorman PG**, Peters ES, Schwartz AG, Terry P, Abbott SE, Camacho F, Wang F, Schildkraut JM. Premenopausal hysterectomy and risk of ovarian cancer in African American women. *Am J Epidemiol* 2017; 186: 46-53.
105. Qin B, **Moorman PG**, Alberg AJ, Barnholtz-Sloan JS, Bondy M, Cote ML, Funkhouser E, Peters ES, Schwartz AG, Terry P, Schildkraut JM, Bandera EV. Dairy, calcium, vitamin D and ovarian cancer risk in African American women. *Br J Cancer* 2016; 115: 1122-1130. (PMCID: PMC5117784)

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108. Peres LC, **Moorman PG**, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Peters ES, Schwartz AG, Terry PD, Abbott SE, Camacho F, Wang F, Schildkraut JM. Lifetime number of ovulatory cycles and epithelial ovarian cancer risk in African American women. *Cancer Causes Control* 2017; 28: 405-14. (PMCID: PMC5410663)
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110. Kelemen LE, Abbott S, Qin B, Peres LC, **Moorman P**, Wallace K, Bandera E, Barnholtz-Sloan J, Bondy M, Cartmell K, Cote M, Funkhouser E, Paddock L, Peters E, Schwartz A, Terry P, Alberg A, Schildkraut J. Cigarette smoking and the association with serous ovarian cancer in African American women: African American Cancer Epidemiology Study (AACES). *Cancer Causes Control* 2017; 28: 699-708.
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112. McNamara C, Abbott SE, Bandera EV, Qin B, Peres LC, Camacho F, **Moorman PG**, Alberg A, Barnholtz-Sloan JS, Bondy M, Cote ML, Funkhouser E, Peters ES, Schwartz AG, Schildkraut JM, Terry P. Tubal ligation and ovarian cancer risk in African-American women. *Cancer Causes Control* 2017; 28: 1033-41.(PMCID: PMC5635599)
113. Barrett NJ, Ingraham KL, Vann Hawkins T, **Moorman PG**. Engaging African Americans in research: the recruiter's perspective. *Ethn Dis* 2017; 27: 453-462. (PMCID: PMC5720956)
114. DeBono NL, Robinson WR, Lund J, Tse CK, **Moorman PG**, Olshan AF, Troester MA. Race, menopausal hormone therapy and invasive breast cancer in the Carolina Breast Cancer Study. *J Women's Health* 2018; 27: 3770386.
115. Abbott SE, Camacho F, Peres LC, Alberg AJ, Bandera EV, Bondy M, Cote ML, Funkhouser E, **Moorman PG**, Peters ES, Qin B, Schwartz AG, Barnholtz-Sloan J, Terry P, Schildkraut JM. Recreational physical activity and survival in African American women with ovarian cancer. *Cancer Causes Control* 2018; 29: 77-86.
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- ovarian cancer: A pooled analysis of 12 case-control studies. *Int J Epidemiol* 2017; 47: 460-472.
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 118. Freedman JA, Wang Y, Li X, Liu H, **Moorman PG**, George DJ, Lee NH, Hyslop T, Wei Q, Patierno SR. Single nucleotide polymorphisms of stemness pathway genes predicted to regulate RNA splicing, microRNA and oncogenic signaling are associate with prostate cancer survival. *Carcinogenesis* 2018; 39: 879-888.
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 122. Qian D, Liu H, Wang X, Ge J, Luo S, Patz EF Jr, **Moorman PG**, Su L, Shen S, Christiani DC, Wei Q. Potentially functional genetic variants in the complement-related immunity gene-set are associated with non-small cell lung cancer survival. *Int J Cancer* 2018, in press.

Letters

1. **Moorman PG**. Letter re: Breast cancer risk factors. *Drug Topics*. 2002; 146: 16.
2. **Moorman PG**. Letter re: Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. *JAMA*. 2004; 292: 1426.
3. Schildkraut JM, **Moorman PG**, Calingaert B, Berchuck A. Letter re: Cyclin E overexpression relates to ovarian cancer histology but not to risk factors. *Cancer Epidemiol Biomarkers Prev*. 2008; 17: 1841-2.
4. **Moorman PG**. Letter re: Age at Menopause: Imputing age at menopause for women with a hysterectomy with application to risk of postmenopausal breast cancer. *Annals Epidemiol*. 2011; 21: 797.
5. Myers ER, **Moorman P**, Sanders GD. Response re: Breast cancer screening: benefit or harm? *JAMA* 2016; 315: 1402-3.
6. Trabuco EC, **Moorman PG**, Cliby WA. In reply re: Association of ovary-sparing hysterectomy with ovarian reserve. *Obstet Gynecol* 2016; 128: 655-6.

Book Chapters and Invited Papers

1. **Moorman PG**, Hames CG, Tyroler HA. Socioeconomic status and morbidity and mortality in hypertensive blacks. In Brest AN and Saunders E (eds): *Cardiovascular Clinics: Cardiovascular Diseases in Blacks*. FA Davis Company, Philadelphia, 1991, 179-93.
2. **Moorman PG**, Hulka BS. Menopausal hormones and the risk of breast cancer. *Endocrinologist*. 1992; 2: 189-94. (Article was awarded annual editorial prize by journal.)
3. Hulka BS, **Moorman PG**. Breast cancer: Hormones and other risk factors, *Maturitas*. 2001; 38: 103-13.
4. **Moorman PG**, Terry PD. Dairy products and breast cancer. 2003. United Kingdom Dairy Council. (Invited paper)
5. **Moorman PG**, Berchuck A. Comment on: Hormone replacement therapy does not increase risk for ovarian cancer in women with BRCA mutations. *North American Menopause Society First to Know*. Feb. 15, 2006. www.menopause.org/news.html.
6. **Moorman PG**, Hamilton RJ. Statins and cancer risk: what do we know and where do we go from here? *Epidemiology*. 2007; 18: 194-6. (Invited paper)
7. Hulka BS, **Moorman PG**. Breast cancer: hormones and other risk factors. *Maturitas*. 2008; 61: 203-213.
(Republished 2001 article of same title in an issue of the journal's top 10 downloaded articles for the period 2000-2008).
8. **Moorman PG**. Ovarian failure after pre-menopausal hysterectomy. *European Obstetrics & Gynecology*. 2012; 7: 35-8. (Invited paper)
9. **Moorman PG**. Genetic markers for ovarian cancer risk: are we close to seeing a clinical impact? *Personalized Medicine*. 2012; 9: 565-7. (Invited paper)
10. **Moorman PG**. Should women at high risk for cancer use oral contraceptive pills? *Personalized Medicine*. 2015, 12: 533-5. (Invited paper)

Technical Reports

1. **Moorman PG**, Goldstein K, Coeytaux R, Myers ER, Strauss J, Van Houtven C, Shepherd-Banigan M, Brancu M, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Nutritional needs of older women. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.
2. Myers ER, Strauss J, Van Houtven C, Goldstein K, Shepherd-Banigan M, Brancu M, **Moorman PG**, Coeytaux R, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Maternal Health. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.
3. Strauss J, Brancu M, Myers ER, Anderson S, Van Houtven C, Goldstein K, Shepherd-Banigan M, **Moorman PG**, Coeytaux R, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Women's Mental Health. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.

4. Goldstein K, Coeytaux R, Myers ER, Strauss J, Van Houtven C, Shepherd-Banigan M, Brancu M, **Moorman PG**, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Girls' Health and Obesity. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.
5. Shepherd-Banigan M, Van Houtven C, Brancu M, Goldstein K, **Moorman PG**, Strauss J, Coeytaux R, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Myers ER, Sanders-Schmidler G. Topic Brief: Family Caregivers for Older Adults. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.

Non-authored Publications (acknowledged for contributions)

1. Newman B, Millikan RC, King M-C. Genetic epidemiology of breast and ovarian cancers. *Epidemiol Rev.* 1997; 19: 69-79.
2. Millikan R, Pittman G, Tse C-K, Savitz DA, Newman B, Bell D. Glutathione S-transferases M1, Ti, and P1 and breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2000; 9: 567-73.
3. Krajcik RA, Massardo S, Orentreich N. No association between serum levels of tumor necrosis factor- α (TNF- α) or the soluble receptors sTNFR1 and sTNFR2 and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2003; 12: 945-6.
4. Trivers KF, Stewart SL, Peipins L, Rim SH, White MC. Expanding the public health research agenda for ovarian cancer. *J Womens Health.* 2009; 18: 1299-305.
5. Soubry A, Il'yasova D, Sedjo R, Wang F, Byers T, Rosen C, Yashin A, Ukraintseva S, Haffner S, D'Agostino R Jr. Increase in circulating levels of IGF-1 and IGF-1/IGFBP-3 molar ratio over a decade is associated with colorectal adenomatous polyps. *Int J Cancer.* 2012; 131: 512-7.

Presentations and Published Abstracts (selected)

Moorman PG, Newman B, Butler LM, Ostermeyer EA, Friedman LS, Millikan RC, Liu ET, King MC. Inherited susceptibility at BRCA1 in a population-based sample. Society for Epidemiologic Research, Boston, MA, June 1996

Rockhill B, Newman B, **Moorman P**, Millikan R, Weinberg C. Summary attributable fraction and breast cancer risk factors. Society for Epidemiologic Research, Boston, MA, June 1996.

Furberg H, Newman B, **Moorman P**, Millikan R. Lactation and breast cancer risk. Society for Epidemiologic Research, Edmonton, Alberta, Canada, June 1997.

Marcus PM, Newman B, Millikan RC, **Moorman PG**, Baird DD, Sternfeld B, Qaqish B. The association of adolescent body mass index (BMI) and physical activity with breast cancer risk. Society for Epidemiologic Research, Edmonton, Alberta, Canada, June 1997.

Huang WY, Newman B, Millikan RC, Schell MJ, **Moorman PG**. Hormone-related factors and risk of breast cancer by estrogen receptor and progesterone receptor status. Society for Epidemiologic Research, Chicago, MD, 1998.

Hall IJ, Newman B, Millikan RC, **Moorman PG**. Evaluating body size and breast cancer risk among black women. Society for Epidemiologic Research, Chicago, MD, 1998.

Marcus PM, Newman B, Millikan RC, Baird DD, **Moorman PG**, Qaqish B. Breast cancer epidemiology: the case for adolescent exposures. Society for Epidemiologic Research, Baltimore, MD, 1999.

Moorman PG. Menopausal hormones and risk of breast cancer. Carolina Breast Cancer Study Participant Symposium, Chapel Hill, NC, April 2000

Moorman PG, Jones BA, Millikan RC, Hall IJ, Newman B. Race, anthropometric factors, and stage at diagnosis of breast cancer. Society for Epidemiologic Research, Seattle, WA, June 2000.

Hall IJ, Newman B, Millikan RC, **Moorman PG**. Comparative analysis of breast cancer risk factors among African-American women and white women. Congress of Epidemiology, Toronto, Ontario, Canada, June 2001.

Moorman PG, et al. Nuts and bolts of field studies: things they didn't teach you in school. Congress of Epidemiology, Toronto, Ontario, Canada, June 2001. (Invited talk)

Moorman PG, Calingaert B, Vine M, Halabi S, Berchuck A, Schildkraut JM. Comparison of two methods for calculating lifetime ovulatory cycles. Congress of Epidemiology, Toronto, Ontario, Canada, June 2001.

Plummer P, Jackson S, Konarski J, Mahanna E, Dunmore C, Regan G, Mattingly D, Parker B, Williams S, Andrews C, Vannappagari V, Hall S, Deming S, Hodgson E, **Moorman P**, Newman B, Millikan R. Making epidemiologic studies responsive to the needs of participants and communities: the Carolina Breast Cancer Study experience. Conference on Breast Cancer and Environmental Mutagens, Research Triangle Park, NC, September 2001.

Moorman PG. Population-based study of breast cancer among African-American and White women in North Carolina. North Carolina Central University, Durham, NC, January 2003. (Invited talk)

Moorman PG. Medication use and breast cancer risk. Psychiatry and Behavioral Sciences Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, NY, March 2003. (Invited talk)

Sansbury L, Millikan R, Schroeder J, **Moorman P**, North K, Sandler R. Use of non-steroidal anti-inflammatory drugs, cyclooxygenase-2 Val411Ala polymorphism and association with colon cancer in a population-based study of African Americans and whites. 3rd Annual AACR International Conference, Seattle, WA, October 2004.

Schildkraut JM, Berchuck A, Murphy S, Marks J, **Moorman P**, Calingaert B, Halabi S. Trinucleotide repeat polymorphisms in the androgen receptor gene and risk of ovarian cancer. 3rd Annual AACR International Conference, Seattle, WA, October 2004.

Moorman PG, Sesay J, Nwosu V, Millikan R. Non-steroidal anti-inflammatory drugs, COX2 polymorphism and breast cancer: a study of gene-environment interactions. Triangle Cancer and Disparities Symposium, North Carolina Central University, Durham, NC, March 2005.

Moorman PG. Racial disparities in breast cancer: problem or opportunity? Johnson C. Smith University, Charlotte, NC, September 2005. (Invited talk)

Trivers K, Gammon M, Abrahamson P, Lund MJ, Kaufman J, **Moorman P**, Cai JW, Porter P, Brinton L, Eley JW. Reproductive factors and breast cancer survival in women less than 55 years of age. 4th Annual Conference on Frontiers in Cancer Prevention Research, Baltimore, MD, November 2005.

Moorman PG. The role of epidemiology in the drug development process. University of Ferrara, Ferrara, Italy, May 2006. (Invited talk)

Moorman PG. Racial disparities in breast cancer: risk factors through survival. Women's Health Research Symposium - Untying the Pink Ribbon: Advances in Breast Cancer. University of Maryland School of Medicine. Baltimore, MD, March 2008. (Invited talk)

Moorman PG, JM Schildkraut JM, ES Iversen ES, ER Myers ER, M Gradison M1, N Warren-White N, F Wang. Weight gain after pre-menopausal hysterectomy. Society for Epidemiologic Research, Chicago, IL, June 2008.

Moorman PG. Non-steroidal anti-inflammatory drugs (NSAIDs) as chemopreventives for cancer: are they ready for prime time? Genetics and Environmental Mutagenesis Society 26th Annual Fall Meeting. Research Triangle Park, NC, October 2008. (Invited talk)

Moorman PG. Introduction to cancer epidemiology. Osher Lifelong Learning Institute lecture series. Chapel Hill, NC, September 2009. (Invited talk)

Moorman PG. Challenges of epidemiologic research in the genomic era: the example of ovarian cancer. Environmental Mutagen Society Annual Meeting, St. Louis, MO, October 2009 (Invited talk)

Moorman PG. Epidemiology in clinical research: beyond randomized controlled trials. Duke University Health System Clinical Education and Professional Development Series, Durham, NC, January 2010. (Invited talk)

Moorman PG. Epidemiology in clinical research: beyond randomized controlled trials. Association of Clinical Research Professionals, Durham, NC, June 2010. (Invited talk)

Moorman PG. The role of epidemiology in understanding disparities in breast cancer. Duke Oncology Symposium – Advances in Surgical and Treatment Options for Breast and Colorectal Cancer. Raleigh, NC, May 2011. (Invited talk)

Østbye T, **Moorman P.** Measurement dilemmas: validity, reliability and messy data. Family Medicine Research Seminar Series, Duke University Medical Center, December 2011.

Moorman P, Østbye T. Research that can tell you something: internal and external validity in study design. Family Medicine Research Seminar Series, Duke University Medical Center, November 2011.

Myers ER, Havrilesky LJ, Gierisch J, **Moorman PG**, Dinan MA, Coeytaux R, Urrutia RP, Lowery WJ, Hasselblad V, McBroom AJ, Sanders GD. Using net benefits and acceptability curves to quantify uncertainty about tradeoffs between harms and benefits of oral contraceptives. Society for Medical Decision Making, Phoenix, AZ, October 2012.

Myers ER, Havrilesky LJ, Gierisch J, **Moorman PG**, Dinan MA, Coeytaux R, Urrutia RP, Lowery WJ, Hasselblad V, McBroom AJ, Sanders GD. Net effects of current patterns of oral contraceptive use on potentially fatal outcomes in the United States. Society for Medical Decision Making, Phoenix, AZ, October 2012.

Stouder A, Melcher B, Morgan PA, **Moorman PG**, Lin L, Stem J. Satisfaction Guaranteed? An Analysis of Lecturer Characteristics Associated with Physician Assistant Student Satisfaction. Physician Assistant Education Association Annual Education Forum, Seattle, WA, November 2012.

Moorman PG. The African American Cancer Epidemiology Study (AACES). Ovarian Cancer in Women of African Ancestry Emerging Consortium Meeting. Bethesda, MD, April 2013.

Moorman PG. Ovarian Cancer: What You Need to Know. Duke Cancer Institute, Cancer Awareness Workshop. Durham, NC, May, August and October 2014.

Moorman PG. Ovarian Cancer in African American Women: The Challenges of Studying a Less Common

Cancer in a Minority Population. Duke Cancer Institute Cancer Control and Population Sciences Seminar Series. Durham, NC, July 2014.

CONSULTANT APPOINTMENTS

National Institutes of Health, Center for Scientific Review

- Epidemiology and Disease Control Subcommittee 2 (EDC-2): Oct. 2000, Feb. 2001
- Special Emphasis Panels: Nov. 2001, Mar. 2002, Nov. 2002, Nov. 2003, July 2004, Nov. 2004, June 2005, Mar. 2006, Nov. 2006, Mar. 2007, July 2007, Nov. 2008, June 2009, July 2009, July 2010, Oct. 2010, Sept. 2011, Dec. 2013, Mar. 2017, Nov. 2017
- Small Grants Program for Cancer Epidemiology: Nov. 2001, Mar. 2003, June 2016, Mar. 2017, June 2017, June 2018, Nov. 2018
- National Cancer Institute, Program Project Review: Jan. 2003, Aug. 2003, Dec. 2003.
- SPORE (Specialized Program of Research Excellence) Review: Breast Cancer Feb. 2005, Ovarian Cancer June 2008, Feb. 2009.

Centers for Disease Control and Prevention. Defining the Public Health Research Agenda for Ovarian Cancer. Invited panel participant. Nov. 2008.

Susan G. Komen for the Cure, Study Section Chair for Post-Doctoral Fellowship in Risk and Prevention, 2010.

Susan G. Komen Breast Cancer Foundation, Study Section Chair for Risk, Prevention and Epidemiology, Member of Programmatic Review Committee, 2005 – 2007.

Susan G. Komen for the Cure/Susan G. Komen Breast Cancer Foundation, Scientific Reviewer, 2003 - 2011.

Department of Defense Breast Cancer Research Program Scientific Peer Review, 1998, 2005, 2007, 2008, 2009, 2013.

Department of Defense Breast Cancer Research Program, Study Section Chair for Training - Epidemiology and Prevention, 2013.

Department of Defense Ovarian Cancer Research Program Scientific Peer Review, 2015, 2016.

Department of Defense Ovarian Cancer Research Program, Study Section Chair for Investigator Initiated Research II, 2018.

National Cancer Institute, Center for Global Health, Data Monitoring Committee for United States – Latin American Cancer Research Network, 2013

CODA, Inc., Research Triangle Park, NC. IRB member, 2004.

National Institute of Environmental Health Sciences Special Emphasis Panel, Technical Evaluation of Support Services for Epidemiology, NIEHS Epidemiology Branch. May 1998.

PROFESSIONAL AWARDS AND SPECIAL RECOGNITIONS

Honorary Physician Assistant, Duke University Medical Center Physician Assistant Program - 2018

Certificate of Appreciation, Duke University Medical Center Physician Assistant Program – 2008

Delta Omega, Public Health Honorary – 1994

The Endocrinologist, Editorial Prize for Volume II – 1993

Research Service Award, National Cancer Institute - 1988-91

Edward E. Smismann Award for Medicinal Chemistry, University of Kansas – 1980

Walter F. Enz Award for Pharmaceutical Chemistry, University of Kansas – 1980

Watkins-Berger Scholarship, University of Kansas - 1975-1980

State of Kansas Scholarship, University of Kansas - 1976-1980

ORGANIZATIONS AND PARTICIPATION

University of North Carolina School of Public Health Alumni Association, Epidemiology Section President, 2001-2002.

Society for Epidemiologic Research

American Pharmaceutical Association

TEACHING RESPONSIBILITIES

Courses Taught

Evidence Based Medicine-I, Duke University, Department of Community and Family Medicine, Physician Assistant program. Primary instructor, 2004-2017.

Evidence Based Medicine-II, Duke University, Department of Community and Family Medicine, Physician Assistant program. Co-Instructor, 2003-2018.

Evidence Based Medicine-I, Duke University, Department of Community and Family Medicine, Physician Assistant program. Lecturer and seminar instructor, 2003.

Epidemiology and Research Methods (PAP 255), Duke University, Department of Community and Family Medicine, Physician Assistant program. Seminar instructor, 2001-2002.

Epidemiology of Cancer (CDE 532B), Yale University, Department of Epidemiology and Public Health. Course director, 1997-2000.

Co-developer of departmental Master's Comprehensive Examination, University of North Carolina-Chapel Hill, Department of Epidemiology, 1995-1996.

Cancer Epidemiology (EPID 233), University of North Carolina-Chapel Hill, Department of Epidemiology, Teaching Assistant, 1992-1993.

Principles of Epidemiology (EPID 160), University of North Carolina-Chapel Hill, Department of Epidemiology, Teaching Assistant, 1990.

Student Mentoring

Helena Furberg, MSPH, University of North Carolina, 1996, Committee Member

Pamela M. Marcus, PhD, University of North Carolina, 1997, Committee Member

Stella Chang, MPH, Yale University, 1997, Committee Member
Mary Riciutti, MPH, Yale University, 1999, Committee Chair
Edward A. Lew, MPH, Yale University, 1999, Committee Member
Shelley Goodstine, MPH, Yale University, 1999, Committee Member
Rupal Desai, MPH, Yale University, 1999, Committee Member
Pei-Yu Lin, MPH, Yale University, 2000, Committee Chair
Lisa Calvocoressi, Ph.D., Yale University, 2003, Dissertation Reader
Rebecca Cleveland, Ph.D., University of North Carolina, 2003, Committee Member
Leah Sansbury, Ph.D., University of North Carolina, 2004, Committee Member
Sumitra Shantakumar White, Ph.D., University of North Carolina, 2006, Committee Member
Katrina Trivers, Ph.D., University of North Carolina, 2006, Committee Member
Amy Dailey, Ph.D., Yale University, 2006, Dissertation Reader
Enid Rivera, M.D., Duke University, 2008, 3rd year Medical Student Preceptor
Alexis Gaines, Duke University, 2013, Master's Committee Member
Chioma Erundu, Duke University, 2013-14, 3rd year Medical Student Preceptor
Tolulope Teniola, Duke University 2016-17, 3rd year Medical Student Preceptor
Tengteng Wang, University of North Carolina, 2018, Committee Member

COMMITTEES AND SERVICE

Standing Committee on Misconduct in Research, Duke University School of Medicine, 2017-present
Senior Faculty Advisory Committee, Office for Research Mentoring, Duke University School of Medicine, 2016-present
Academy of Mentors, Office of Faculty Mentoring, Duke University School of Medicine, 2014-16
Society for Epidemiologic Research. Reviewer for Tyroler and Lilienfeld Prize Papers, 2015
Appointments, Promotions and Tenure Committee, Department of Community and Family Medicine, Duke University Medical Center. Committee Member, 2008-2018
Quality Assurance Sub-Committee for Clinical Research Units, Duke University Medical Center, Committee Chair, 2013-2014
Quality Assurance Sub-Committee for Clinical Research Units (formerly Site-based Research Units), Duke University Medical Center, Committee Member, 2011-2013
Path to Independence Faculty Mentoring Program, Duke University School of Medicine, Peer Reviewer, 2012-2018
Society for Epidemiologic Research. Abstract reviewer for annual meeting, 2011
Cancer Prevention, Detection and Control Research Program, Duke University Medical Center, Cancer Control Pilot Study application reviewer, 2010, 2011

Executive Council, Department of Community and Family Medicine, Duke University Medical Center
2009-present

Education Committee, Department of Community and Family Medicine, Duke University Medical Center,
2009-2017

Faculty Search Committee, Cancer Prevention, Detection and Control Research Program, 2010

Duke Cancer Institute, Editorial Advisory Committee Member, 2010-2011

Duke Comprehensive Cancer Center Annual Meeting, Judge for poster presentations, 2009

Director Search Committee, Cancer Prevention, Detection and Control Research Program, 2009

Partners Allied in Research (PAIR) Pilot Grant application reviewer, Cancer Prevention, Detection and
Control Research Program, 2005

Editorial Reviewer

American Journal of Epidemiology
Archives of Gynecology and Obstetrics
Breast Diseases
Cancer
Cancer Causes and Control
Cancer Research
Epidemiology
Gynecologic Oncology
International Journal of Epidemiology
Journal of Community Development
J of the Women's American Medical Assn
Lancet
Nutrition and Cancer
Public Health Nutrition
Women and Health

Annals of Epidemiology
Breast Cancer Research and Treatment
British Medical Journal-Cancer
Cancer Biomarkers
Cancer Epidemiology Biomarkers and Prevention
Clinical Breast Cancer
Ethnicity and Disease
International Journal of Cancer
JAMA
Journal of the National Cancer Institute
Journal of Women's Health
Lancet Oncology
Pharmacogenomics
Trends in Molecular Medicine

CURRENT RESEARCH

Epidemiology of breast and ovarian cancer
Ovarian function after hysterectomy
Racial differences in disease risk and outcomes
Medication use and cancer risk
Etiologic factors for uterine fibroids

EXTERNAL SUPPORT - PAST

Principal Investigator	% effort	Title of Project and Funding Source	Total Costs	Duration
Barbara Hulka	25%	High-Density Lipoprotein Cholesterol and Breast Cancer, National Cancer Institute, R03, Supported dissertation research	\$72,234	1992 – 1993

Beth Newman	100%	Carolina Breast Cancer Study, Project 2 SPORE in Breast Cancer, National Cancer Institute, P50.	\$1,275,000	1992 – 1995
Beth Newman	50%	Carolina Breast Cancer Study, Project 2 SPORE in Breast Cancer, National Cancer Institute, P50.	\$2,511,146	1995 - 1996
Patricia Moorman	50%	Medication Use and Breast Cancer in a Bi-racial Population, National Cancer Institute, R29-FIRST Award.	\$498,302	1996 – 2002
Patricia Moorman	0%	Carolina Breast Cancer Study Participant Symposium, North Carolina Division of American Cancer Society Small Grant.	\$2500	1997
Patricia Moorman	0%	Carolina Breast Cancer Study Participant Symposium, Susan G. Komen Breast Cancer Foundation Small Grant.	\$5000	1997
Joellen Schildkraut	10%	Carolina Georgia Center, Cancer Genetics Network, National Cancer Institute, U-24.	\$4,028,129	2002 – 2004
Patricia Moorman	0%	Non-steroidal Anti-Inflammatory Drugs and Breast Cancer: A Study of Gene-Environment Interactions among African-American and White Women, Minority Serving Institution Partnership Grant, Pilot Funds.	\$28,040	2003 – 2004
Celette Skinner	5%	Partnerships to Eliminate Disparities in Cancer Outcomes and Research, National Cancer Institute, National Cancer Institute.	\$517,743	2002 – 2006
Patricia Moorman	0%	Diversity Supplement to RO1 AG020162 Ovarian Failure Among Hysterectomized Women, National Institute on Aging (Note: Grant was awarded but post-doc accepted another position.)	\$169,720	2006
Andrew Berchuck	5%	Biological Basis for Chemoprevention of Ovarian Cancer, Department of Defense.	\$824,000	2002 – 2007
Stephen Freedland	5%	Weight Loss and Gain and Cancer Free Survival after Radical Prostatectomy in a Multiethnic Cohort. Prostate Cancer Foundation.	\$100,000	2007-2009
Joellen Schildkraut	10%	Genetic Modifiers of BRCA1 and BRCA2, Project 3 SPORE in Breast Cancer. National Cancer Institute.	\$1,795,862	2003 – 2009
Joellen Schildkraut	10%	Molecular Epidemiology of Ovarian Cancer. National Cancer Institute.	\$3,750,000	2003 – 2010

Patricia Moorman	40%	Ovarian Failure among Hysterectomized Women. National Institute on Aging.	\$3,781,480	2003 - 2010
Patricia Moorman (Sub-contract PI)	3%	Cancer Genetics Network. National Cancer Institute.	~\$25,000	2010 – 2012
Laura Havrilesky	15%	Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer. Agency for Healthcare Research and Quality	\$486,476	2010 - 2012
Jeffrey Marks	5%	Atlantic Breast and Gynecologic Clinical Validation Center. National Cancer Institute	>\$1,500,000	2010 - 2013
Cathrine Hoyo	5%	Disparities in Cervical Cancer Precursors and Deregulation of Imprinted Genes National Cancer Institute	~\$200,000	2012 – 2013
Emanuel Trabuco (Moorman, Duke PI)	2%	Anti-Müllerian Hormone as a Marker of Ovarian Reserve in Women with and without Hysterectomy. Mayo Clinic Internal Funds	\$100,000	2012 – 2013
Evan Myers	10%	Systematic Review of Cancer Screening Literature for Updating American Cancer Society Breast Cancer Screening Guidelines American Cancer Society	~\$400,000	2013 - 2014
Joellen Schildkraut	9%	Cancer Education and Career Development Training Grant. National Cancer Institute	~\$1,400,000	2009 – 2014
Patricia Moorman (Sub-contract PI)	5%	Rare Cancer Genetics Network National Cancer Institute	~\$240,000	2010 – 2016
Joellen Schildkraut (Moorman, co-PI)	20%	Epidemiology of Ovarian Cancer in African American Women National Cancer Institute	~\$12,000,000	2010 – 2017
Gillian Sanders	10%	Management of Infertility Evidence-Based Practice Center		2015-2016
Gillian Sanders	10%	Management of Labor Dystocia Evidence-Based Practice Center		2016
Gillian Sanders	15%	Office of Women’s Health – Topic Development Evidence-Based Practice Center		2016
Evan Myers	5%	Comparing Management Options for Management: Patient-centered Results for Uterine Fibroids (COMPARE-UF) PCORI	~\$19,000,000	2014 – 2018

EXTERNAL SUPPORT - CURRENT

Principal Investigator	% effort	Title of Project and Funding Source	Total Costs	Duration
Joellen Schildkraut (Moorman, sub- contract PI)	13%	Exploring Factors Related to Racial Disparities in Ovarian Cancer Incidence and Survival: The OCWAA (Ovarian Cancer in Women of African Ancestry) Consortium National Cancer Institute	~\$450,000	2017 - 2021

PERSONAL INFORMATION

Work address: DUMC Box 2715, 2424 Erwin Road, Suite 602, Durham, NC 27705

Work phone #: (919) 681-4557

E-mail address: patricia.moorman@duke.edu

Home address: 3 Skipwith Court, Durham, NC 27707

Home phone #: (919) 419-9301

Marital status: Married

Spouse's name: Allan R. Moorman, Ph.D.

Exhibit 7

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

-----X

IN RE: JOHNSON & JOHNSON

TALCUM POWDER PRODUCTS	MDL No.:
MARKETING, SALES PRACTICES,	
AND PRODUCTS LIABILITY	16-2738 (FLW)(LHG)
LITIGATION	

THIS DOCUMENT RELATES TO
ALL CASES

-----X

VIDEOTAPED DEPOSITION OF
PATRICIA G. MOORMAN, M.S.P.H., PH.D.

FRIDAY, JANUARY 25, 2019

9:04 A.M.

Taken by the Defendants
at Cambria Hotel & Suites Durham
2306 Elba Street
Durham, North Carolina 27705

- - -

Reported by Sophie Brock, RPR, RMR, RDR, CRR

- - -

GOLKOW LITIGATION SERVICES
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 2	Page 4
<p>1 APPEARANCES</p> <p>2 ON BEHALF OF THE PLAINTIFFS:</p> <p>3 ASHCRAFT & GEREL, LLP</p> <p>4 4900 Seminary Road</p> <p>5 Alexandria, Virginia 22311</p> <p>6 Telephone: (703) 931-5500</p> <p>7 By: MICHELLE A. PARFITT, ESQ.</p> <p>8 mparfitt@ashcraftlaw.com</p> <p>9 - and -</p> <p>10 MUELLER LAW, LLC</p> <p>11 404 W 7th Street</p> <p>12 Austin, Texas 78701</p> <p>13 Telephone: (512) 478-1236</p> <p>14 By: STEVE FARIES, ESQ.</p> <p>15 steve.faries@muellerlaw.com</p> <p>16 - and -</p> <p>17 NAPOLI SHKOLNIK PLLC</p> <p>18 400 Broadhollow Road, Suite 305</p> <p>19 Melville, New York 11747</p> <p>20 Telephone: (631) 224-1133</p> <p>21 By: ALASTAIR J.M. FINDEIS, ESQ.</p> <p>22 afindeis@napolilaw.com</p> <p>23 ON BEHALF OF THE DEFENDANTS JOHNSON & JOHNSON:</p> <p>24 SHOOK, HARDY & BACON L.L.P.</p> <p>25 600 Travis Street, Suite 3400</p> <p>Houston, Texas 77002</p> <p>Telephone: (713) 227-8008</p> <p>By: SCOTT A. JAMES, ESQ.</p> <p>sjames@shb.com</p> <p>- and -</p> <p>DRINKER BIDDLE & REATH, LLP</p> <p>600 Campus Drive</p> <p>Florham Park, New Jersey 07932-1047</p> <p>Telephone: (973) 549-7164</p> <p>By: JESSICA L. BRENNAN, ESQ.</p> <p>jessica.brennan@dbr.com</p>	<p>1 INDEX OF EXAMINATIONS</p> <p>2 PAGE</p> <p>3 BY MR. JAMES 9, 302, 315</p> <p>4 BY MS. FOSTER 280</p> <p>5 BY MS. APPEL 294</p> <p>6 BY MS. PARFITT 310</p> <p>7</p> <p>8 INDEX OF EXHIBITS</p> <p>9 NUMBER DESCRIPTION MARKED</p> <p>10 Exhibit 1 Invoices of Patricia G. Moorman, ...15</p> <p>11 Ph.D.</p> <p>12 Exhibit 2 Errata Page from Deposition17</p> <p>13 Transcript of Patricia Moorman,</p> <p>14 Ph.D.</p> <p>15 Exhibit 3 Curriculum Vitae of Patricia20</p> <p>16 Moorman, M.S.P.H, Ph.D.</p> <p>17 Exhibit 4 Notice of Oral and Videotaped32</p> <p>18 Deposition of Patricia G. Moorman</p> <p>19 and Duces Tecum</p> <p>20 Exhibit 5 Binder of Materials Considered ...35</p> <p>21 Exhibit 6 Plaintiffs' Steering Committee's ...36</p> <p>22 Response and Objections to the</p> <p>23 Notice of Oral and Videotaped</p> <p>24 Deposition of Patricia G. Moorman</p> <p>25 and Duces Tecum</p> <p>Exhibit 7 Rule 26 Expert Report of Patricia ...37</p> <p>G. Moorman, M.S.P.H., Ph.D.</p> <p>Exhibit 8 Additional Materials to41</p> <p>Dr. Patricia Moorman</p> <p>Exhibit 9 Reliance Materials of Patricia ...45</p> <p>Moorman, Ph.D., Produced March 5,</p> <p>2018</p>
Page 3	Page 5
<p>1 APPEARANCES (Continued)</p> <p>2 ON BEHALF OF THE DEFENDANT IMERYS TALC AMERICA, INC.:</p> <p>3 GORDON & REES, LLP</p> <p>4 816 Congress Avenue, Suite 1510</p> <p>5 Austin, Texas 78701</p> <p>6 Telephone: (512) 391-0197</p> <p>7 By: JENNIFER A. FOSTER, ESQ.</p> <p>8 jfooster@gordonrees.com</p> <p>9 - and -</p> <p>10 COUGHLIN DUFFY LLP</p> <p>11 350 Mount Kemble Avenue</p> <p>12 Morristown, New Jersey 07962</p> <p>13 Telephone: (973) 267-0058</p> <p>14 By: JONATHAN F. DONATH, ESQ.</p> <p>15 jdonath@coughlinduffy.com</p> <p>16 ON BEHALF OF THE DEFENDANT PERSONAL CARE PRODUCTS</p> <p>17 COUNCIL:</p> <p>18 SEYFARTH SHAW LLP</p> <p>19 975 F Street, N.W.</p> <p>20 Washington, DC 20004-1454</p> <p>21 Telephone: (202) 463-2400</p> <p>22 By: RENÉE B. APPEL, ESQ.</p> <p>23 rappel@seyfarth.com</p> <p>24 ON BEHALF OF THE DEFENDANT PTI:</p> <p>25 TUCKER ELLIS LLP</p> <p>233 South Wacker Drive</p> <p>Chicago, Illinois 60606</p> <p>Telephone: (312) 624-6300</p> <p>By: JAMES W. MIZGALA, ESQ.</p> <p>james.mizgala@tuckerellis.com</p> <p>VIDEOGRAPHER:</p> <p>Brad Smith</p>	<p>1 INDEX OF EXHIBITS (Continued)</p> <p>2 NUMBER DESCRIPTION MARKED</p> <p>3 Exhibit 10 References and Materials49</p> <p>4 Considered List for the MDL Report</p> <p>5 Exhibit 11 Deposition Transcript of Patricia ...61</p> <p>6 Moorman, M.S.P.H., Ph.D., dated</p> <p>7 March 12, 2018</p> <p>8 Exhibit 12 FDA Action Related to Talc77</p> <p>9 Exhibit 13 FDA Letter dated April 1, 2014 ...84</p> <p>10 Exhibit 14 IARC Monographs Document titled ...91</p> <p>11 "Arsenic, Metals, Fibres, and</p> <p>12 Dusts, Volume 100 C, A Review of</p> <p>13 Human Carcinogens"</p> <p>14 Exhibit 15 AACR Journal Article titled "Does ... 107</p> <p>15 Exposure to Asbestos Cause Ovarian</p> <p>16 Cancer? A Systematic Literature</p> <p>17 Review and Meta-analysis," by</p> <p>18 Alison Reid, et al.</p> <p>19 Exhibit 16 American Journal of Epidemiology ... 136</p> <p>20 Article titled "Ovarian Cancer Risk</p> <p>21 Factors in African-American and</p> <p>22 White Women," by Patricia G.</p> <p>23 Moorman, et al.</p> <p>24 Exhibit 17 Cancer Causes Control Article ... 139</p> <p>25 titled "Primary peritoneal and</p> <p>ovarian cancers: an epidemiological</p> <p>comparative analysis," by Delores</p> <p>J. Grant, et al.</p> <p>Exhibit 18 Printout from ACOG's Website: 149</p> <p>"Talc Use and Ovarian Cancer"</p>

2 (Pages 2 to 5)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 6			Page 8		
1	INDEX OF EXHIBITS (Continued)		1	P R O C E E D I N G S	
2	NUMBER	DESCRIPTION MARKED	2	THE VIDEOGRAPHER: We are now on	
3	Exhibit 19	National Cancer Institute PDQ 151	3	record. Today's date is January 25th, 2019, and the	
4		titled "Ovarian, Fallopian Tube,	4	time is approximately 9:04 a.m. This is the	
5		and Primary Peritoneal Cancer	5	videotaped deposition of Dr. Patricia Moorman.	
6	Exhibit 20	Epidemiology Article titled 165	6	Could counsel please now introduce	
7		"Perineal Talc Use and Ovarian	7	themselves for the record, and then our court reporter	
8		Cancer, A Systematic Review and	8	will swear in the witness.	
9	Exhibit 21	Review Article titled "Genital . . . 169	9	MR. JAMES: Scott James for the Johnson	
10		use of talc and risk of ovarian	10	& Johnson Defendants.	
11		cancer: a meta-analysis," by	11	MS. BRENNAN: Jessica Brennan for the	
12		Wera Berge, et al.	12	Johnson & Johnson Defendants.	
13	Exhibit 22	Research Report titled "Perineal . . 173	13	MS. FOSTER: Jennifer Foster for Imerys	
14		use of talc and risk of ovarian	14	Talc America, Inc.	
15		cancer," by H. Langseth, et al.	15	MR. DONATH: Jonathan Donath for Imerys	
16	Exhibit 23	Anticancer Research Article 175	16	Talc, Inc.	
17		titled "Perineal Application of	17	MS. APPEL: Renée Appel, here for	
18		Cosmetic Talc and Risk of Invasive	18	Personal Care Products Council.	
19		Epithelial Ovarian Cancer: A	19	MR. MIZGALA: James Mizgala for PTI.	
20		Meta-analysis of 11,933 Subjects	20	MR. FINDEIS: Alastair Findeis,	
21		from Sixteen Observational	21	Plaintiffs' Steering Committee.	
22		Studies," by Michael Huncharek,	22	MR. FARIES: Steve Faries for the	
23		et al.	23	Plaintiffs.	
24	Exhibit 24	AACR Journal Research Article 180	24	MS. PARFITT: Michelle Parfitt for the	
25		titled "Genital Powder Use and Risk	25	Plaintiffs.	
		of Ovarian Cancer: A Pooled			
		Analysis of 8,525 Cases and 9,859			
		Controls," by Kathryn L. Terry,			
		et al.			
	Exhibit 25	JNCI Article titled "Perineal 202			
		Powder Use and Risk of Ovarian			
		Cancer," by Serena C. Houghton,			
		et al.			

Page 7			Page 9		
1	INDEX OF EXHIBITS (Continued)		1	Whereupon,	
2	NUMBER	DESCRIPTION MARKED	2	PATRICIA G. MOORMAN, M.S.P.H., PH.D.	
3	Exhibit 26	Journal of the National Cancer . . . 205	3	having first been duly sworn/affirmed,	
4		Institute Article, titled	4	was examined and testified as follows:	
5		"Prospective Study of Talc Use and	5	EXAMINATION BY COUNSEL FOR THE	
6	Exhibit 27	PLOS ONE Research Article titled . . 227	6	JOHNSON & JOHNSON DEFENDANTS	
7		"Comparison of Estimates between	7	BY MR. JAMES:	
8		Cohort and Case-Control Studies in	8	Q. Good morning, Dr. Moorman.	
9		Meta-Analyses of Therapeutic	9	A. Good morning.	
10	Exhibit 28	AACR Journal Research Article . . . 234	10	Q. My name is Scott James. We've had the	
11		titled "Association between Body	11	pleasure of meeting before the deposition. I'm	
12		Powder Use and Ovarian Cancer: The	12	counsel for the J&J Defendants in this matter.	
13		African American Cancer	13	Do you understand that?	
14	Exhibit 29	AACR Journal Article titled "Body . . 237	14	A. I do.	
15		Powder and Ovarian Cancer Risk -	15	Q. Super. Could you state your name for the	
16	Exhibit 30	International Journal of Cancer . . . 273	16	record, please.	
17		Article titled "Perineal Talc	17	A. My name is Patricia Moorman.	
18		Exposure and Epithelial Ovarian	18	Q. And you have been deposed before in a talc	
19		Cancer Risk in the Central Valley	19	ovarian cancer case; correct?	
20		of California," by Paul K. Mills,	20	A. Yes, I have.	
21		et al.	21	Q. And you've testified on behalf of the	
22	Exhibit 31	Paper titled "Systematic Review . . . 307	22	Plaintiffs in that case; correct?	
23		and Meta-Analysis of the	23	A. Yes, I did.	
24		Association between Perineal Use of	24	Q. And the allegations in that case were that	
25		Talc and Risk of Ovarian Cancer,"	25	cosmetic talc powders cause ovarian cancer; correct?	
		by Mohamed Kadry Taher, et al.			

3 (Pages 6 to 9)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 10	Page 12
<p>1 A. That's correct.</p> <p>2 Q. You were deposed in the Ingham case.</p> <p>3 Do you recall the name of the case?</p> <p>4 A. Yes, I do.</p> <p>5 Q. And you were last deposed in that case in</p> <p>6 March of 2018. Do you recall that?</p> <p>7 A. Yes, I do.</p> <p>8 Q. Has there been any change in your employment</p> <p>9 status since your March 2018 deposition?</p> <p>10 A. I am still a professor at Duke University,</p> <p>11 yes.</p> <p>12 Q. Has there been any change in your work or</p> <p>13 teaching activities since your deposition?</p> <p>14 A. Yes.</p> <p>15 Q. What are those changes?</p> <p>16 A. I am in a preretirement transition, and so</p> <p>17 I have been reducing my effort. And so I do not --</p> <p>18 I'm not doing as much teaching as I was a year ago.</p> <p>19 Q. Other than that fairly significant change,</p> <p>20 are there any other changes in your teaching or work</p> <p>21 activities since the deposition?</p> <p>22 A. No.</p> <p>23 Q. Have you done any new expert witness work</p> <p>24 since the last deposition other than the talc MDL that</p> <p>25 we're here about today?</p>	<p>1 A. I'm afraid I'm a little bit unclear about the</p> <p>2 particular cases. I understand that this is an MDL</p> <p>3 case. I have been in touch with attorneys about</p> <p>4 various cases since, you know, 2016, but I'm a little</p> <p>5 bit unclear about the distinctions.</p> <p>6 Q. In preparing for today's deposition for the</p> <p>7 talc MDL, did you meet with counsel?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. And who did you meet with?</p> <p>10 A. I have met with the individuals here,</p> <p>11 Michelle Parfitt, Steve Faries, Alastair, and -- I'm</p> <p>12 blanking on his last name all of a sudden -- and Jeff</p> <p>13 Gibson.</p> <p>14 Q. Are those the only attorneys that you've met</p> <p>15 with regard to your deposition today?</p> <p>16 A. Yes.</p> <p>17 Q. In preparing your MDL talc report, are there</p> <p>18 any other attorneys that you worked with other than</p> <p>19 the ones that you just mentioned with regard to the</p> <p>20 MDL?</p> <p>21 MS. PARFITT: Objection. Form.</p> <p>22 You may answer.</p> <p>23 I just wanted to make sure that -- I believe</p> <p>24 he's asking the names of people, not the</p> <p>25 communications.</p>
Page 11	Page 13
<p>1 A. No, I have not.</p> <p>2 Q. And you understand that we are taking your</p> <p>3 deposition today in the talc MDL; correct?</p> <p>4 A. Yes.</p> <p>5 Q. Who first contacted you about serving as an</p> <p>6 expert in the talc MDL?</p> <p>7 A. It was -- let's see -- Jeff Gibson was the</p> <p>8 first person who contacted me about talc litigation.</p> <p>9 Q. When you say "talc litigation," are you</p> <p>10 referring to the Ingham case?</p> <p>11 A. I'm afraid that I'm a little unclear on --</p> <p>12 you know, there are multiple attorneys, multiple</p> <p>13 cases, and I don't know who was the Defendant and when</p> <p>14 he first approached me.</p> <p>15 Q. Understood.</p> <p>16 A. Or the Plaintiff, rather. I'm sorry.</p> <p>17 Q. Do you recall the time frame that Mr. Gibson</p> <p>18 contacted you?</p> <p>19 A. It was in summer of 2016.</p> <p>20 Q. Are you retained in any talc cases other than</p> <p>21 the talc MDL and the Ingham case?</p> <p>22 A. Not to my knowledge, no.</p> <p>23 Q. Sitting here today, do you have the ability</p> <p>24 to distinguish as to whether any attorney contacted</p> <p>25 you specifically about the talc MDL?</p>	<p>1 MR. JAMES: Yes.</p> <p>2 THE WITNESS: Okay. I believe that on</p> <p>3 teleconferences, Chris Tisi was also on one of the --</p> <p>4 at least one of the teleconferences, probably more</p> <p>5 than one.</p> <p>6 BY MR. JAMES:</p> <p>7 Q. Was Mr. Tisi involved in teleconferences</p> <p>8 pertaining to the report that you authored?</p> <p>9 A. Yes.</p> <p>10 Q. And, again, I'm not asking you about the</p> <p>11 substance of the communications, just the</p> <p>12 identification of the attorneys that you've worked</p> <p>13 with. Okay?</p> <p>14 A. Okay.</p> <p>15 Q. Are there any other attorneys that you've</p> <p>16 worked with on the MDL report?</p> <p>17 A. None that I recall.</p> <p>18 Q. Are you working with any of the counsel that</p> <p>19 you just identified on any other litigation or</p> <p>20 matters?</p> <p>21 A. No, I am not.</p> <p>22 Q. Okay. Today at the deposition, we'll follow</p> <p>23 the same ground rules as the Ingham deposition. So</p> <p>24 I know that you're familiar with them, but as a</p> <p>25 reminder, my questions will be verbal and I ask that</p>

4 (Pages 10 to 13)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 14	Page 16
<p>1 your answers be verbal as well. Okay?</p> <p>2 A. Okay.</p> <p>3 Q. And that's so the court reporter can take</p> <p>4 down what you're saying and can take down what I'm</p> <p>5 saying as well.</p> <p>6 Also, Michelle has told you this, but</p> <p>7 anytime you need a break, just let us know and we'll</p> <p>8 be happy to accommodate you. Okay?</p> <p>9 A. Okay.</p> <p>10 Q. And if you have any -- if you have any -- let</p> <p>11 me rephrase that.</p> <p>12 If you don't understand any questions that</p> <p>13 I ask you, please ask me to rephrase. Okay?</p> <p>14 A. Okay.</p> <p>15 Q. Great.</p> <p>16 What are you charging Plaintiffs' counsels</p> <p>17 in the MDL?</p> <p>18 A. My rate is \$400 per hour.</p> <p>19 Q. How much have you invoiced in the MDL to</p> <p>20 date?</p> <p>21 A. For the MDL, I believe it is 21,000.</p> <p>22 Q. Okay. And prior -- sorry. Did I cut you</p> <p>23 off?</p> <p>24 A. No, you did not.</p> <p>25 Q. This morning, your counsel handed me a copy</p>	<p>1 MS. PARFITT: And I've just got to add</p> <p>2 some clarity to that.</p> <p>3 MR. JAMES: Sure.</p> <p>4 MS. PARFITT: There might be some</p> <p>5 overlap. I think that's the problem. There might</p> <p>6 just be some overlap.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. Are there any invoices that you have prepared</p> <p>9 for your work in the talc litigation that you have not</p> <p>10 produced to us today in the MDL, be it Exhibit 1 or in</p> <p>11 your work in Ingham?</p> <p>12 A. These are the only invoices related to the</p> <p>13 talc litigation, period.</p> <p>14 Q. And do you have an estimate of -- when you</p> <p>15 say that these are the only invoices for the talc</p> <p>16 litigation -- and if these questions continue to be</p> <p>17 confusing, let me know -- but are there other invoices</p> <p>18 that you submitted in the Ingham case that are not</p> <p>19 part of Exhibit 1?</p> <p>20 A. No. These are all the invoices submitted.</p> <p>21 Q. We got there finally. Sorry about that.</p> <p>22 A. Okay.</p> <p>23 Q. Have you discussed your work in this</p> <p>24 litigation with any other experts who are working on</p> <p>25 behalf of the Plaintiffs?</p>
Page 15	Page 17
<p>1 of the invoices that you furnished in the MDL, and I'm</p> <p>2 going to mark this as Exhibit No. 1.</p> <p>3 (Exhibit No. 1 was marked for identification.)</p> <p>4 BY MR. JAMES:</p> <p>5 Q. Exhibit No. 1 is containing four invoices.</p> <p>6 I'm going to hand those to you and ask you to confirm</p> <p>7 that those are the invoices that you have prepared for</p> <p>8 your work in the MDL.</p> <p>9 A. There are some for -- that work that was done</p> <p>10 with the Ingham case, and my understanding, that's not</p> <p>11 part of the MDL.</p> <p>12 Q. That's fair. Yes.</p> <p>13 A. Okay.</p> <p>14 Q. So are the invoices that I've handed you as</p> <p>15 part of Exhibit 1, are those the invoices related to</p> <p>16 the work that you've done on the MDL?</p> <p>17 A. I -- I'm sorry. I'm -- I'm trying to answer</p> <p>18 your question, but the ones for prior -- other than</p> <p>19 the Ashcraft & Gerel, my understanding was that these</p> <p>20 were for, like, the Ingham case and the state cases,</p> <p>21 not the MDL.</p> <p>22 Q. Okay. Let me ask it this way: Are these the</p> <p>23 invoices that you've submitted to Michelle Parfitt?</p> <p>24 A. They've been submitted to the people noted on</p> <p>25 there. So --</p>	<p>1 A. No. To my knowledge, I have not.</p> <p>2 Q. Have you had any emails or other</p> <p>3 communications with Plaintiffs' experts in the talc</p> <p>4 litigation?</p> <p>5 A. No, I have not.</p> <p>6 Q. And you recall giving your testimony in the</p> <p>7 Ingham case in March 2018; correct?</p> <p>8 A. Yes, I do.</p> <p>9 Q. After that testimony that you provided, you</p> <p>10 also had an opportunity to review that testimony;</p> <p>11 correct?</p> <p>12 A. I did.</p> <p>13 Q. And do you recall preparing a single</p> <p>14 correction to the Ingham transcript?</p> <p>15 A. Yes.</p> <p>16 Q. And so I have with me a copy of what we refer</p> <p>17 to as an errata sheet, which is the correction sheet</p> <p>18 that you signed in Ingham. I'm going to mark that as</p> <p>19 Exhibit No. 2. Okay?</p> <p>20 (Exhibit No. 2 was marked for identification.)</p> <p>21 BY MR. JAMES:</p> <p>22 Q. And the way that we're configured, there's</p> <p>23 some space between me and your counsel. So when</p> <p>24 I have exhibits, as I will throughout the day --</p> <p>25 we may have to figure out how to approach this, but I</p>

5 (Pages 14 to 17)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 18	Page 20
<p>1 may hand them to you and ask that you hand them over 2 since we're all miked up. 3 Okay. And do you recognize your handwriting 4 on that Exhibit? 5 A. I do. 6 Q. Does that reflect the correction that you 7 made to your testimony? 8 A. Yes, it does. 9 Q. And if you flip over to the other side of 10 Exhibit 2, does that contain your signature? 11 A. Yes, it does. 12 Q. By signing that errata sheet, you confirmed 13 that the testimony that you gave in Ingham was true 14 and correct; correct? 15 A. Yes. 16 Q. Do you still stand behind the testimony that 17 you provided in Ingham today? 18 A. Yes, I do. 19 Q. Subject to the one correction that you made; 20 correct? 21 A. Yes, I do. 22 Q. Sitting here today, do you believe there are 23 any other changes or corrections that you need to make 24 to your testimony in Ingham? 25 A. I can't think of any, no.</p>	<p>1 A. I am. 2 Q. Okay. So for purposes of the record, this 3 morning, before the deposition, your counsel handed me 4 a copy of your updated CV. 5 Is that what you're looking at right now? 6 A. Yes, it is. 7 Q. Okay. I'm going to mark a copy of that as 8 Exhibit No. 3. 9 (Exhibit No. 3 was marked for identification.) 10 MR. JAMES: Michelle, you have a copy, 11 I presume? 12 MS. PARFITT: Actually, I think I gave 13 them all to you. Sorry. 14 MR. JAMES: Again, apologies for having 15 to handle it that way. 16 THE WITNESS: Oh, I'm sorry. 17 MS. PARFITT: Thank you. 18 THE WITNESS: Okay. The article that 19 I was referring to is -- the first author is Park. 20 The title of the article is "Benign gynecologic 21 conditions are associated with ovarian cancer risk in 22 African-American women: A case-control study." 23 And I was a coauthor on that paper, and talc 24 was included as a potential confounder. 25</p>
Page 19	Page 21
<p>1 Q. Did you review your Ingham deposition in 2 preparation for today's deposition? 3 A. I did within the last few weeks, yes. 4 Q. And so when you've reread the transcript in 5 the last few weeks, did you see anything in that 6 transcript that you wanted to correct? 7 A. No. 8 Q. Since your Ingham deposition in March of 9 2018, have you authored any publications or articles 10 pertaining to talc, asbestos, or ovarian cancer risk 11 factors? 12 A. Yes, I have. 13 Q. Okay. And let's break up that, then. 14 Have you authored any articles pertaining to 15 talc? 16 A. I have not authored any articles that 17 directly address talc as the main focus of the paper. 18 Talc has been mentioned in at least one paper as a 19 potential confounder. 20 Q. And what was the name of that article, 21 please. 22 A. If you'll give me just a moment, let me 23 look -- 24 Q. Dr. Moorman, are you looking at a copy of 25 your CV?</p>	<p>1 BY MR. JAMES: 2 Q. And, for the record, can you tell us the 3 number of the item you're looking at on your CV? 4 A. Okay. On page 14, it is Article No. 120. 5 Q. And in that paper, Dr. Moorman, did you say 6 that you described talc as a potential confounder? 7 A. Yes. 8 Q. In that paper, did you include a disclosure 9 of your involvement in this talc litigation as an 10 expert for the Plaintiffs? 11 A. I disclosed it -- actually, I had a 12 discussion with the senior author on this paper, who's 13 Michele Cote, and disclosed what I was doing. And she 14 was -- she actually said she had also done some work 15 related to talc and ovarian cancer and she was going 16 to check with the editor and see if it required a 17 disclosure. And so there was no disclosure. So 18 apparently the editor did not feel it was warranted. 19 Q. So the article, as published, does not 20 contain a disclosure of your involvement in the 21 litigation; correct? 22 A. That is correct. 23 Q. Did you review the disclosure requirements of 24 the journal in which the article was published? 25 A. I can't remember if I specifically looked at</p>

6 (Pages 18 to 21)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 22	Page 24
<p>1 that journal's requirements. I don't recall if I did 2 or not.</p> <p>3 Q. Do you believe that it is important -- for an 4 author who's working on an article for a publication 5 pertaining to an issue that she's testifying about in 6 litigation, do you believe it's important to disclose 7 that to the reader of the article?</p> <p>8 A. I think that it is important to disclose it 9 in conjunction with the journal's policies, as I 10 described. I did disclose it to the corresponding 11 author, who said she was going to discuss it with the 12 editor. So I think that I did what was appropriate.</p> <p>13 Q. Did you communicate your involvement in the 14 litigation to anyone with the journal?</p> <p>15 A. I did not. It is typical that the 16 communication with the journal is through the 17 corresponding author.</p> <p>18 Q. Have you attempted to amend any disclosures 19 in your prior papers since the last deposition?</p> <p>20 MS. PARFITT: Objection. Form.</p> <p>21 THE WITNESS: I do --</p> <p>22 MR. JAMES: You're looking at your 23 counsel. Michelle can correct me if I'm wrong. She's 24 allowed to make the objections. And once she does, 25 unless she tells you not to answer, you may answer.</p>	<p>1 Q. Did they communicate with you about the 2 disclosure in a written format?</p> <p>3 A. It was an email communication.</p> <p>4 Q. Was it a single email, or was it multiple 5 emails?</p> <p>6 A. As I recall, I sent an email to the editor 7 disclosing the situation, and he -- I think he 8 responded that, yes, it should be disclosed. And then 9 I believe there was another email from -- I don't 10 know -- an editorial assistant or someone asking 11 specifically what was the -- what was the wording of 12 the disclosure that I wanted to make, and I gave them 13 that.</p> <p>14 So it was, you know, two or three emails, 15 but...</p> <p>16 Q. Do you still have that email traffic in your 17 possession?</p> <p>18 A. Probably.</p> <p>19 Q. It's on your computer?</p> <p>20 A. I would think so.</p> <p>21 Q. Okay. Could you ensure that you preserve 22 that email traffic for us, please.</p> <p>23 A. Yes.</p> <p>24 MR. JAMES: And then, Michelle, we will 25 request a copy of the email traffic.</p>
Page 23	Page 25
<p>1 MS. PARFITT: That's fine.</p> <p>2 THE WITNESS: Okay. Yes. In my last 3 deposition, there was an article that I was one of 40 4 authors that looked at about 20 different risk factors 5 for ovarian cancer. I acknowledged in my deposition 6 that it was an oversight. In my career, you know, 7 spanning 25 years, I've never had to make disclosures 8 about potential conflicts of interest. I acknowledged 9 that it was an oversight on my part. When it was 10 brought to my attention, I contacted the journal, and 11 they said, "Okay. What's your disclosure?" And 12 I disclosed it.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. So just to be clear, this was after the 15 deposition; correct?</p> <p>16 A. It was.</p> <p>17 Q. Is this the Peres paper?</p> <p>18 A. Yes.</p> <p>19 Q. Did they respond to you in any way about the 20 reported conflict?</p> <p>21 A. The editor just said, "Okay. What is your 22 disclosure?"</p> <p>23 And I gave it to him. And I believe that 24 they subsequently published a correction to the 25 article.</p>	<p>1 MS. PARFITT: We'll certainly take it 2 under advisement, sure.</p> <p>3 BY MR. JAMES:</p> <p>4 Q. Do you have any similar written 5 communications about the disclosure with the paper 6 that we just discussed, the Park paper?</p> <p>7 A. No, I do not. That was a telephone 8 conference.</p> <p>9 Q. Other than the Park article that you just 10 identified, have you authored any other articles since 11 your last deposition concerning talc, asbestos, or 12 risk factors for ovarian cancer?</p> <p>13 A. As you can see on my CV, since the last 14 deposition, Article No. 121 is a paper on effect of 15 cultural, folk, and religious beliefs on delays in 16 diagnosis of ovarian cancer. I was first author on 17 that paper.</p> <p>18 Article 119, first author Anderson, was 19 looking at individual, social, and societal correlates 20 of health-related quality of life among 21 African-American survivors of ovarian cancer.</p> <p>22 And I was a coauthor on a paper by Mills 23 that was looking at immune regulatory molecular 24 expression.</p> <p>25 Q. Since your Ingham deposition, have you</p>

7 (Pages 22 to 25)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 26	Page 28
<p>1 authored any articles that pertain to talc or asbestos 2 other than the Park article? 3 A. No. 4 Q. Are you currently working on any articles or 5 publications that pertain to the issues addressed in 6 your expert report? 7 A. I am a coauthor on a paper that is in 8 preparation that is describing the OCWAA Consortium, 9 which stands for Ovarian Cancer in Women of African 10 Ancestry. And this is a relatively newly formed 11 consortium, and it's describing the overall structure 12 of the consortium and some of the factors that we 13 intend to consider. And in the draft of the paper, 14 talc is included along with a long list of other risk 15 factors that we will be considering. 16 Q. Is that paper in draft form? 17 A. It is in draft form. It's being -- yeah, it 18 has not been submitted yet. 19 Q. So it has not been submitted for peer review? 20 A. No, it has not. 21 Q. Is talc mentioned in the context of a 22 potential confounder, like the Park paper? 23 MS. PARFITT: Object to form. 24 THE WITNESS: Talc is mentioned in that 25 paper as one of many ovarian cancer risk factors that</p>	<p>1 communications or written paperwork about your 2 conflict for that paper? Your litigation disclosure 3 for that paper? Is there anything in writing about 4 that to anyone or the journal itself, or a journal? 5 A. At this point, no, because it is still in 6 draft form. It's not ready to be submitted. 7 Q. Okay. Other than the papers we have 8 discussed this morning, are there any other papers 9 that you -- that are works in progress that discuss 10 talc or asbestos that you're working on? 11 A. Another paper that is in progress is looking 12 at infertility as a risk factor for ovarian cancer. 13 And talc is, again, considered as a potential 14 confounder of that association. 15 So, again, draft form. It hasn't been 16 disclosed yet because it's not at the point where one 17 would disclose that. 18 Q. Okay. And you answered my next question, and 19 that's fine. So thank you. 20 Can you identify the coauthors on the paper 21 that you've just -- that you just mentioned, the 22 infertility paper? 23 A. The infertility paper? Okay. This was work 24 that was done with a medical student, Tolu Teniola is 25 the medical student that I was working with. And then</p>
Page 27	Page 29
<p>1 we hope to examine in this -- within this consortium. 2 BY MR. JAMES: 3 Q. So one of the purposes of that paper, as 4 you've described, is that you will be looking at the 5 association between talc and ovarian cancer; is that 6 correct? 7 MS. PARFITT: Objection. Form. 8 THE WITNESS: It is -- the purpose of 9 the paper is to describe the consortium. So there is 10 relatively little data about risk factors for ovarian 11 cancer among African -- African-American women, or 12 women of African ancestry. And so the purpose of the 13 paper is not focused just on talc, but it is 14 describing how the consortium hopes to compare risk 15 factors for ovarian cancer between African-American 16 and white women. So talc is among a long list of risk 17 factors that will be considered as we progress with 18 this consortium. 19 BY MR. JAMES: 20 Q. Have you yet disclosed your involvement in 21 the litigation with respect to that paper? 22 A. The -- I will disclose it when the paper will 23 be submitted, which is the typical time when such a 24 disclosure would be made. 25 Q. Have you engaged in any written</p>	<p>1 all of the AACES -- this is, again, African American 2 Cancer Epidemiology Study, which is an ovarian cancer 3 study that I've worked on for about the last nine or 4 ten years, and so all of the collaborators on that 5 study. 6 And when you look at the CV, the papers that 7 come from AACES, it's Dr. Schildkraut, Dr. Bondy, 8 Dr. Cote. It's a large multicenter study; there are 9 many coauthors, and so they would all be included. 10 Q. And with respect to the other 11 work-in-progress paper that you have identified, can 12 you identify the coauthors on that paper. 13 MS. PARFITT: Are you speaking of the 14 infertility paper? 15 MR. JAMES: The first question was 16 about the infertility. So now we're back to the first 17 work-in-progress paper that you identified. 18 THE WITNESS: Okay. So the study 19 describing the OCWAA Consortium, is that what you're 20 asking me about? 21 BY MR. JAMES: 22 Q. Yes, Doctor. Thank you for clearing that up. 23 A. Okay. So it includes -- again, this is a 24 multicenter study -- quite a few coauthors. They 25 would include Dr. Schildkraut, Lynn Rosenberg, Traci</p>

8 (Pages 26 to 29)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 30	Page 32
<p>1 Bethea, Wendy Setiawan.</p> <p>2 Again, it's a large consortium with a lot of</p> <p>3 coauthors. There would be probably at least a dozen,</p> <p>4 probably more.</p> <p>5 Q. For both work-in-progress papers, are you</p> <p>6 aware of whether any of those coauthors are experts</p> <p>7 for the Plaintiffs in the talc litigation?</p> <p>8 A. I am not aware of -- if any of them are.</p> <p>9 Q. Have you -- are there any other works in</p> <p>10 progress that pertain to talc or asbestos that you're</p> <p>11 working on?</p> <p>12 A. No, I do not believe so.</p> <p>13 Q. Have you submitted the substance of your</p> <p>14 opinions in the MDL report to anyone for peer review?</p> <p>15 A. No, I have not.</p> <p>16 Q. Have you engaged in any internet postings,</p> <p>17 blogs, chatroom postings concerning your opinions in</p> <p>18 this litigation?</p> <p>19 A. No, I have not.</p> <p>20 Q. Have you given any presentations, speeches,</p> <p>21 or lectures concerning talc or asbestos or ovarian</p> <p>22 cancer risk factors since your March 2018 deposition?</p> <p>23 A. No, I have not.</p> <p>24 Q. Have you given any interviews, public</p> <p>25 statements, or other public speaking engagements</p>	<p>1 communications with your professional colleagues about</p> <p>2 your opinions?</p> <p>3 A. No, I have not.</p> <p>4 Q. And when I say "about your opinions," I mean</p> <p>5 about your opinions in this litigation.</p> <p>6 Is there any written communications, emails,</p> <p>7 or other writings expressing your opinions in this</p> <p>8 litigation to your professional colleagues?</p> <p>9 A. No, I do not believe so.</p> <p>10 Q. Have you had any discussions, since your</p> <p>11 Ingham deposition, with any healthcare professionals</p> <p>12 who treat ovarian cancer patients about your</p> <p>13 litigation opinions?</p> <p>14 A. No, I have not.</p> <p>15 Q. Have you prepared any letters to the editor</p> <p>16 about any of the publications that you cite in your</p> <p>17 MDL report?</p> <p>18 A. No, I have not.</p> <p>19 Q. Okay. I am going to hand you a copy of the</p> <p>20 deposition notice for this case. I'm going to mark</p> <p>21 that as Exhibit No. 4.</p> <p>22 (Exhibit No. 4 was marked for identification.)</p> <p>23 MR. JAMES: Michelle, do you need a</p> <p>24 copy?</p> <p>25 MS. PARFITT: I believe I might have</p>
Page 31	Page 33
<p>1 concerning talc, asbestos, or ovarian cancer risk</p> <p>2 factors since your Ingham deposition?</p> <p>3 A. No, I have not.</p> <p>4 Q. Since your Ingham deposition -- and I'm</p> <p>5 structuring my questions sometimes this way in hopes</p> <p>6 of expediting. Okay?</p> <p>7 So since your Ingham deposition, have you</p> <p>8 discussed your opinions in this litigation with any of</p> <p>9 your professional colleagues?</p> <p>10 A. To some extent, yes.</p> <p>11 Q. Okay. And can you tell me who that is?</p> <p>12 A. I already mentioned Dr. Cote, Michele Cote,</p> <p>13 described the work that I was doing.</p> <p>14 I have mentioned some of the work that I'm</p> <p>15 doing to some of my colleagues within my department,</p> <p>16 Dr. Truls Ostbye for one, Dr. Kat Pollak for another.</p> <p>17 Q. And when you say that you've mentioned your</p> <p>18 litigation work with your department colleagues, what</p> <p>19 have you told them?</p> <p>20 A. I have basically described that I have been</p> <p>21 working as an expert witness in this -- in this case,</p> <p>22 and expressing my opinion, you know, that -- working</p> <p>23 for the Plaintiffs and my opinion that talc is a cause</p> <p>24 of ovarian cancer.</p> <p>25 Q. And have you engaged in any written</p>	<p>1 given you mine. If you would be so kind, I appreciate</p> <p>2 that.</p> <p>3 MR. JAMES: Dr. Moorman.</p> <p>4 THE WITNESS: Thank you.</p> <p>5 BY MR. JAMES:</p> <p>6 Q. Okay. Dr. Moorman, have you seen the</p> <p>7 deposition notice that I just handed you before?</p> <p>8 A. Yes, I have.</p> <p>9 Q. Okay. And you understand from your prior</p> <p>10 deposition, that this is a document that formally</p> <p>11 notices the time and place and why we're here; right?</p> <p>12 A. Yes.</p> <p>13 Q. And if you turn to page 3 of the notice, you</p> <p>14 see that there is a section for definitions, and then</p> <p>15 it follows with a list of document requests; correct?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. And your counsel this morning has</p> <p>18 produced to me a copy of your invoices, a copy of your</p> <p>19 updated CV, an additional-materials-considered list,</p> <p>20 and has also indicated that the references to your MDL</p> <p>21 report are going to be available to us on a thumb</p> <p>22 drive.</p> <p>23 Other than those materials that I just</p> <p>24 described, are there any other materials that you've</p> <p>25 brought with you today that respond to this deposition</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 34	Page 36
<p>1 notice?</p> <p>2 A. No, there are no other documents.</p> <p>3 MR. JAMES: Michelle, is there anything</p> <p>4 else that you brought with you that is responsive to</p> <p>5 the deposition notice?</p> <p>6 MS. PARFITT: You know, the only thing</p> <p>7 that might -- I believe you asked this, Mr. James --</p> <p>8 any notes that she might have taken.</p> <p>9 MR. JAMES: Yes, I was going to ask</p> <p>10 that.</p> <p>11 MS. PARFITT: So why don't we just wait</p> <p>12 for that. I do have something for that.</p> <p>13 MR. JAMES: Okay. Fair enough.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. Dr. Moorman, did you provide to your counsel</p> <p>16 any working copies of materials that you've reviewed</p> <p>17 for purposes of preparing your report or preparing for</p> <p>18 today's deposition?</p> <p>19 A. Can you tell me what you mean by "working</p> <p>20 copies"?</p> <p>21 Q. Sure. Have you made any notes on any of the</p> <p>22 materials that you reviewed for purposes of your work</p> <p>23 on the MDL?</p> <p>24 A. Yes. In this notebook here, there are</p> <p>25 articles. Most of them are the epidemiologic studies.</p>	<p>1 in your possession that are not contained in this</p> <p>2 binder?</p> <p>3 A. No. It's there and the report. That's it.</p> <p>4 MS. PARFITT: Mr. James, if we could,</p> <p>5 do you mind, could she have that back? In the event</p> <p>6 you start to ask her questions about it, she may want</p> <p>7 hers instead, and then we'll make sure you get it.</p> <p>8 Thank you.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. And before we commenced this morning, your</p> <p>11 counsel, Ms. Parfitt, handed me a copy of the</p> <p>12 objections that they have lodged -- that the</p> <p>13 Plaintiffs have lodged to the deposition.</p> <p>14 MR. JAMES: Ms. Parfitt, do you want to</p> <p>15 mention that on the record?</p> <p>16 MS. PARFITT: Yes. If we could kindly</p> <p>17 have marked as Exhibit No. -- I believe it's 6 now.</p> <p>18 This is the Plaintiffs Steering Committee's Response</p> <p>19 and Objections to the Oral and Video Deposition of</p> <p>20 Dr. Patricia Moorman.</p> <p>21 Thank you.</p> <p>22 (Exhibit No. 6 was marked for identification.)</p> <p>23 BY MR. JAMES:</p> <p>24 Q. Dr. Moorman, I'm just going to hand you a</p> <p>25 copy of this because it looks like you're keeping a</p>
Page 35	Page 37
<p>1 And on some of them, I have notes that basically help</p> <p>2 me kind of categorize and -- categorize the articles</p> <p>3 and some of the main things that they looked at. You</p> <p>4 know, did they address dose-response? Did they look</p> <p>5 at histology? Those types of things. It was just to</p> <p>6 kind of help me sort them out.</p> <p>7 Q. And you brought that binder with you here</p> <p>8 today; correct?</p> <p>9 A. Correct.</p> <p>10 MR. JAMES: Michelle, I'm going to mark</p> <p>11 that as Exhibit No. 5.</p> <p>12 MS. PARFITT: You can. What I would</p> <p>13 ask, last evening we didn't have the ability to get</p> <p>14 everything copied. So what we will do is, we can mark</p> <p>15 that, and we'll make some arrangements to get that</p> <p>16 copied so we can get the originals back to</p> <p>17 Dr. Moorman.</p> <p>18 MR. JAMES: Sure. That's fine.</p> <p>19 So I'm going to mark this binder</p> <p>20 Exhibit No. 5.</p> <p>21 (Exhibit No. 5 was marked for identification.)</p> <p>22 BY MR. JAMES:</p> <p>23 Q. Dr. Moorman, other than what you've provided</p> <p>24 to me in Exhibit No. 5, are there any other notes or</p> <p>25 working copies of materials considered that you have</p>	<p>1 pile over there for us of all the exhibits. Okay?</p> <p>2 I'm not going to ask any questions about it.</p> <p>3 A. Okay.</p> <p>4 Q. Okay. Dr. Moorman, in anticipation -- or in</p> <p>5 preparation for your work on the MDL, or in</p> <p>6 conjunction with your work on the MDL, you also</p> <p>7 authored an expert report; correct?</p> <p>8 A. That is correct.</p> <p>9 Q. I'm going to mark a copy of that as</p> <p>10 Exhibit No. 7. And we'll be talking about this</p> <p>11 throughout the day today. Okay?</p> <p>12 A. Okay.</p> <p>13 (Exhibit No. 7 was marked for identification.)</p> <p>14 Q. Okay. I'm handing you Exhibit 7. Is that a</p> <p>15 copy of your report that you've authored in the MDL?</p> <p>16 A. Yes, it is.</p> <p>17 Q. Do you agree that the report defines the</p> <p>18 scope of the opinions that you intend to offer in the</p> <p>19 MDL?</p> <p>20 A. Yes.</p> <p>21 MS. PARFITT: If I may, Scott, may</p> <p>22 I just see a copy of that report?</p> <p>23 MR. JAMES: I have extra copies as</p> <p>24 well, Michelle. If you need anything, just let me</p> <p>25 know.</p>

10 (Pages 34 to 37)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 38	Page 40
<p>1 MS. PARFITT: Thank you. That would be 2 great. 3 MR. FARIES: I'll be the runner on this 4 one. 5 MR. JAMES: Thank you. 6 BY MR. JAMES: 7 Q. Did you review your report prior to -- in 8 preparation -- let me start that over. 9 Did you review your report in preparation 10 for today's deposition? 11 A. Yes, I did. 12 Q. Are there any changes that you want to make 13 to the report today? 14 A. No, there are not. 15 Q. Did you write the report? 16 A. Yes, I did. 17 Q. Okay. Are all parts of the report in your 18 wording? 19 A. Yes. 20 Q. Okay. If you can turn with me, Dr. Moorman, 21 to page 41. And you see here that there is a list of 22 references; correct? 23 A. Yes. 24 Q. Okay. And if you also turn to page 50, do 25 you see that there's a separate list that begins on</p>	<p>1 transcript for Curtis Omiencinski, I do not recall 2 reviewing that at all. It might have been provided to 3 me, but I don't recall reviewing it. 4 Q. Is there any way sitting here today that we 5 can efficiently identify which items on the additional 6 materials list that you have reviewed and which you 7 haven't? 8 A. I don't know what you mean by "efficiently." 9 You know, it's kind of hard to recall exactly. You 10 know, there are lots of articles here. That might 11 have been provided to me. I don't know how I could go 12 through it in just a few minutes to say did I look at 13 it or not. It would just take some time. 14 Q. Did Plaintiffs' counsel provide you all the 15 items on this list, the additional materials list? 16 A. No, I don't believe so. I mean, some of the 17 articles I've had -- like, again, some of them just 18 kind of jump out at me, like the reference 31, 19 Fathalla, "Incessant ovulation and ovarian cancer, a 20 hypothesis," that is an article that I have probably 21 referred to dozens of times. 22 Q. So the additional materials list contains a 23 mixture of items that you had on your own and items 24 that were provided to you; is that fair? 25 A. That is correct.</p>
Page 39	Page 41
<p>1 page 50, halfway down, that's titled "Additional 2 materials and data considered"? 3 A. I'm sorry -- 4 Q. On page 50. 5 A. -- let me get to the right page. 6 Yes. 7 Q. Can you explain to me the difference between 8 the reference list and the additional materials and 9 data considered list? 10 A. Okay. The reference list are the references 11 to support the opinions and the statements in the 12 report that I wrote. There are some other materials 13 that I was provided, might have read, but they just 14 did not meet the level of actually needing to be 15 referenced in the report to support a certain 16 statement. 17 Some of these I might have read in more 18 detail than others, but I feel like the reference list 19 are the ones that actually supported the statements 20 that I made in my report. 21 Q. As described by you just now, are there items 22 on the additional materials and data considered list 23 that you have not reviewed at all? 24 A. There are -- along the way, there seem to be 25 some -- like, for example, item 62, comparing a</p>	<p>1 Q. Now, do you intend to rely on any materials 2 for your opinions in this case that are not identified 3 in the reference list or the additional materials 4 list? 5 MS. PARFITT: Objection. Form. 6 THE WITNESS: I mean, I am relying on 7 the expertise that I developed over more than 25 years 8 as an epidemiologist. And so there may be 9 publications, knowledge that I have that is not 10 specifically listed here. But, in general, I think 11 that is a fairly comprehensive list. I don't know 12 that I could say that it is completely exhaustive. 13 BY MR. JAMES: 14 Q. All right. I'm going to mark now as 15 Exhibit No. 8 a copy of a list entitled "Additional 16 Materials to Dr. Patricia Moorman." 17 (Exhibit No. 8 was marked for identification.) 18 BY MR. JAMES: 19 Q. Have you seen a copy of Exhibit 8 before, 20 Dr. Moorman? 21 A. I don't think that I have seen this 22 particular list. 23 MS. PARFITT: And for the record, this 24 list was compiled by Plaintiffs' counsel, Mr. James, 25 and I'm not sure whether or not my office -- the</p>

11 (Pages 38 to 41)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 42	Page 44
<p>1 materials were sent, but I'm not sure whether the list 2 was sent to Dr. Moorman. 3 MR. JAMES: Okay. 4 BY MR. JAMES: 5 Q. Looking at this list, Dr. Moorman, this list 6 was furnished to us this week. 7 Do you understand that? 8 MS. PARFITT: Objection. 9 THE WITNESS: I -- if you say so. 10 BY MR. JAMES: 11 Q. Fair enough. This list -- does this list 12 include items that you were provided after you 13 authored your MDL report? 14 A. Yes. 15 Q. This list of materials did not form the 16 opinions that you included in your MDL report; 17 correct? 18 MS. PARFITT: Objection. Form. 19 THE WITNESS: I did not have access, 20 you know, to these expert reports and all before 21 I wrote my report, no. So they did not inform my 22 report. 23 BY MR. JAMES: 24 Q. Have you reviewed the materials on this list 25 as Exhibit No. 8 in their entirety?</p>	<p>1 reports have you reviewed? 2 A. Again, I have reviewed them in different 3 levels of detail and completeness. But I have looked 4 at the report of Anne McTiernan, April 5 Zambelli-Weiner, Daniel Clarke-Pearson, David Kessler, 6 Jack Siemiatycki, Michael Crowley, Rebecca 7 Smith-Bindman, and Sonal Singh, you know, to some 8 extent. 9 And I might have looked at some of the 10 others, but those were the ones that I specifically 11 recall looking at to some extent. 12 Q. Did you ask for Plaintiffs' counsel to 13 furnish you the expert reports in the litigation? 14 A. I did not. They provided them to me without 15 asking. 16 Q. Why did you review the reports of the other 17 experts? 18 A. Intellectual curiosity is the main thing. 19 I'm always interested to learn other people's 20 perspectives. And also to see if there was any 21 additional evidence that I might consider. 22 Q. And after reviewing those reports, did you 23 find any additional evidence that you might consider 24 that you didn't list in your MDL report? 25 A. I really didn't. I thought that there was a</p>
Page 43	Page 45
<p>1 A. No, not in their entirety. 2 Q. Have you reviewed some and not reviewed 3 others? Is that fair? 4 A. I have -- yes, I have reviewed some of them. 5 I have not reviewed all of them. 6 Q. Okay. Is there any way for us to, again, 7 efficiently determine today which of these you've 8 reviewed and which ones you haven't? 9 A. I -- again, I could go through them and, to 10 the best of my knowledge, tell you which ones 11 I reviewed. Again, some of them I reviewed in more 12 detail, read more completely; others I looked at 13 more -- in a more cursory way. 14 Q. Did your review of any of these additional 15 materials change the opinions that you've included in 16 your MDL report? 17 A. No, they did not change my opinion. 18 Q. Did you review all of these expert reports 19 listed? 20 A. I did not review all of them. I reviewed 21 some of them. 22 Q. Okay. And these are the Plaintiffs' expert 23 reports that are listed on this list; correct? 24 A. That is my understanding. 25 Q. Okay. Which of the Plaintiffs' expert</p>	<p>1 remarkable level of consistency in the opinions, 2 particularly among the people who were reviewing the 3 epidemiologic literature. 4 Q. Dr. Moorman, I am going to now hand you a 5 copy of the reliance materials -- which is the title 6 of the list -- that you cited in the Ingham case. 7 Okay? I'm going to mark that as Exhibit No. 9. 8 (Exhibit No. 9 was marked for identification.) 9 BY MR. JAMES: 10 Q. Does that list look familiar to you? 11 A. Yes. 12 Q. And you see on the front of that list, it 13 says it was produced on March 5th, 2018; correct? 14 A. That is correct. 15 Q. And did you prepare this list? 16 A. I did not personally prepare it, no. 17 Q. Do you know that the reliance list that you 18 produced in Ingham and the reliance list that you have 19 attached as a reference list and a materials 20 considered list to your MDL report are substantially 21 different? 22 A. I would -- 23 MS. PARFITT: Objection. Form. 24 THE WITNESS: I would not be surprised 25 to say that there are some different references cited,</p>

12 (Pages 42 to 45)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 46</p> <p>1 yes.</p> <p>2 BY MR. JAMES:</p> <p>3 Q. Do you understand that there's a large number</p> <p>4 of additional references that you have now cited in</p> <p>5 your MDL report?</p> <p>6 A. I -- the reference list is longer, yes.</p> <p>7 Q. Do you have any idea by how much?</p> <p>8 MS. PARFITT: Objection. Form.</p> <p>9 THE WITNESS: No, I do not.</p> <p>10 BY MR. JAMES:</p> <p>11 Q. Would it surprise you to find out that there</p> <p>12 are 94 new items listed in your MDL report that were</p> <p>13 not listed in your March 2018 report?</p> <p>14 MS. PARFITT: Objection. Form.</p> <p>15 THE WITNESS: I -- you know, as you go</p> <p>16 along, I think that it is not unusual to include more</p> <p>17 references. I didn't know the exact number of new</p> <p>18 items.</p> <p>19 BY MR. JAMES:</p> <p>20 Q. Again, did you prepare the lists that are</p> <p>21 attached to your MDL report?</p> <p>22 A. The -- the list of references, I prepared</p> <p>23 that. The list of additional items, I think that was</p> <p>24 a combination of some of what I had prepared and</p> <p>25 I think what counsel had provided to me.</p>	<p style="text-align: right;">Page 48</p> <p>1 have become part of the public domain since that time.</p> <p>2 Do you understand that?</p> <p>3 MS. PARFITT: Objection. Form.</p> <p>4 THE WITNESS: I understand that some of</p> <p>5 them had been published before my deposition in March</p> <p>6 2018.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. Are there specific topics of the new</p> <p>9 materials that you added between your Ingham</p> <p>10 deposition and your MDL report?</p> <p>11 A. I'm trying to think what they might be. I --</p> <p>12 some -- I think that some of the work, for example, by</p> <p>13 Fletcher and Saed describing some of their work</p> <p>14 related to possible biological mechanisms by which</p> <p>15 talc exposure could lead to ovarian cancer -- I think</p> <p>16 that was some work that I, perhaps, had not been aware</p> <p>17 of previously. And so that's one thought that comes</p> <p>18 to mind.</p> <p>19 Q. All of the items that you added from March</p> <p>20 2018 Ingham list to your MDL list, were all of those</p> <p>21 items provided to you by Plaintiffs' counsel?</p> <p>22 MS. PARFITT: Objection. Asked and</p> <p>23 answered.</p> <p>24 THE WITNESS: I don't -- I don't think</p> <p>25 so.</p>
<p style="text-align: right;">Page 47</p> <p>1 Q. When you provided your opinion in March of</p> <p>2 2018 in the Ingham case, did you do so based on a</p> <p>3 comprehensive review of the literature?</p> <p>4 A. I think that -- yes, I believe that it was a</p> <p>5 comprehensive review, particularly of the</p> <p>6 epidemiologic data.</p> <p>7 Q. Why did you expand your list of references</p> <p>8 and materials considered for the MDL?</p> <p>9 A. I think just as you acquire, you know, become</p> <p>10 aware of more references, maybe if there were any new</p> <p>11 publications, or just as I expanded the knowledge,</p> <p>12 I think that it would be appropriate to include more</p> <p>13 references.</p> <p>14 Q. Do you know that a number -- a large number</p> <p>15 of the new references and materials considered were</p> <p>16 available in the public domain or in the -- in this</p> <p>17 litigation at the time that you gave your March 2018</p> <p>18 deposition?</p> <p>19 MS. PARFITT: Objection. Form.</p> <p>20 THE WITNESS: It would not surprise me</p> <p>21 to say that -- to see that some of them were there.</p> <p>22 BY MR. JAMES:</p> <p>23 Q. So, to be clear, the additional materials</p> <p>24 that you have added between March 2018 and your MDL</p> <p>25 report, those materials are not simply materials that</p>	<p style="text-align: right;">Page 49</p> <p>1 BY MR. JAMES:</p> <p>2 Q. Would you say the majority of the items that</p> <p>3 you've added from March 2018 to your MDL report were</p> <p>4 provided to you by Plaintiffs' counsel?</p> <p>5 MS. PARFITT: Objection. Form.</p> <p>6 THE WITNESS: I don't know what</p> <p>7 quantity, what fraction was provided by counsel and</p> <p>8 which I identified.</p> <p>9 MR. JAMES: Okay. I'm going to mark as</p> <p>10 Exhibit No. 10 a copy of your references and materials</p> <p>11 considered list for the MDL report.</p> <p>12 (Exhibit No. 10 was marked for identification.)</p> <p>13 BY MR. JAMES:</p> <p>14 Q. Okay. Dr. Moorman --</p> <p>15 MS. PARFITT: Just one correction,</p> <p>16 Mr. James. I think Exhibit 10 is just identified as</p> <p>17 "references." I believe you characterized it as</p> <p>18 "references and material considered."</p> <p>19 MR. JAMES: Yeah. I think if you keep</p> <p>20 flipping, Michelle -- or Ms. Parfitt -- it contains</p> <p>21 both.</p> <p>22 MS. PARFITT: Fair enough.</p> <p>23 BY MR. JAMES:</p> <p>24 Q. Okay. And you see, Dr. Moorman, if you've</p> <p>25 had a chance to flip through it while counsel have</p>

13 (Pages 46 to 49)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 50	Page 52
<p>1 been talking, you see that this Exhibit 10 includes</p> <p>2 some highlighting; right?</p> <p>3 A. Yes.</p> <p>4 Q. The highlighting, I'll state for the record,</p> <p>5 represents our effort to capture the items that have</p> <p>6 been added between Ingham and your MDL report.</p> <p>7 Do you see that highlighting?</p> <p>8 A. Mm-hmm.</p> <p>9 Q. Again, I think we discussed this earlier, but</p> <p>10 does it surprise you to find out that there are 94 new</p> <p>11 items on the two MDL lists?</p> <p>12 MS. PARFITT: Objection. Asked and</p> <p>13 answered.</p> <p>14 THE WITNESS: Again, I believe that</p> <p>15 I answered that question previously.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. 13 of the 20 references that are new were</p> <p>18 available to you as of March 2018. Did you know that?</p> <p>19 MS. PARFITT: Objection. Asked and</p> <p>20 answered.</p> <p>21 THE WITNESS: Again, I answered the</p> <p>22 question when you asked it previously.</p> <p>23 BY MR. JAMES:</p> <p>24 Q. I don't think that we've talked specifically</p> <p>25 about the references, but the references -- the</p>	<p>1 "search terms" or the primary search that was done, it</p> <p>2 was very simple. It was "talc" or "talcum powder" and</p> <p>3 "ovarian cancer." But many times, the initial search</p> <p>4 will not generate all of the articles that you would</p> <p>5 need to describe the science. There may be additional</p> <p>6 articles, either things that I was aware of or</p> <p>7 different searches that might be done.</p> <p>8 But the overall search term to find the</p> <p>9 literature on talc and ovarian cancer, I did not</p> <p>10 change that.</p> <p>11 Would it be a good time to take a break?</p> <p>12 We've been going for over an hour.</p> <p>13 MR. JAMES: For sure.</p> <p>14 MS. PARFITT: Certainly.</p> <p>15 THE VIDEOGRAPHER: Going off record at</p> <p>16 10:05 a.m.</p> <p>17 (Recess taken from 10:05 a.m. to 10:18 a.m.)</p> <p>18 THE VIDEOGRAPHER: Back on record at</p> <p>19 10:18 a.m.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. Dr. Moorman, are you ready to proceed?</p> <p>22 A. I am.</p> <p>23 Q. Great. Dr. Moorman, do you consider yourself</p> <p>24 to be an expert in animal studies and talc?</p> <p>25 A. No, I do not.</p>
Page 51	Page 53
<p>1 references that you've cited to your MDL report, those</p> <p>2 are materials that you say form the opinions issued in</p> <p>3 your MDL report; correct?</p> <p>4 A. Yes.</p> <p>5 Q. And you added 20 new references from your</p> <p>6 Ingham list to your MDL report. Do you know that?</p> <p>7 A. I know that there are new references, yes.</p> <p>8 Q. And did you know that 13 of the 20 new</p> <p>9 references -- again, the references are the list of</p> <p>10 materials that formed your MDL report -- those were</p> <p>11 available before March 2018? Did you know that?</p> <p>12 A. I am aware that some of them were available.</p> <p>13 Would like to make the point that many of</p> <p>14 the points that I make in my report can be supported</p> <p>15 by many, many references. And so the fact that</p> <p>16 I added new references, that's really not too</p> <p>17 surprising. It's -- again, if I felt like wanted to</p> <p>18 emphasize a point more strongly, including additional</p> <p>19 references, I don't think that would be surprising to</p> <p>20 add additional references.</p> <p>21 Q. Did you change your standards or search terms</p> <p>22 that you used in the Ingham literature review for the</p> <p>23 MDL review?</p> <p>24 MS. PARFITT: Objection to form.</p> <p>25 THE WITNESS: When we talk about</p>	<p>1 Q. Do you consider yourself to be an expert in</p> <p>2 cell studies and talc?</p> <p>3 A. No, I do not.</p> <p>4 Q. Okay. Do you consider yourself to be an</p> <p>5 expert in cytotoxicity studies and talc?</p> <p>6 A. No, I do not.</p> <p>7 Q. Do you consider yourself to be an expert in</p> <p>8 mutagenicity studies and talc?</p> <p>9 A. No, I do not.</p> <p>10 Q. Do you consider yourself to be an expert in</p> <p>11 genotoxicity studies and talc?</p> <p>12 A. No, I do not.</p> <p>13 Q. Do you consider yourself to be an expert in</p> <p>14 mineral testing methods?</p> <p>15 A. No, I do not.</p> <p>16 Q. Okay. Do you consider yourself an expert in</p> <p>17 mineral characterization?</p> <p>18 A. No, I do not.</p> <p>19 Q. Do you consider yourself to be an expert in</p> <p>20 cancer biology?</p> <p>21 A. I am not a cancer biologist; however, I</p> <p>22 consider cancer biology frequently in my work.</p> <p>23 Q. Do you consider yourself to be an expert in</p> <p>24 geology?</p> <p>25 A. No, I do not.</p>

14 (Pages 50 to 53)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 54	Page 56
<p>1 Q. And do you consider yourself to be an expert 2 in mining? 3 A. No, I do not. 4 Q. Do you have expertise in pathology? 5 A. I -- once again, I am not a pathologist. 6 Sometimes rely on pathology and have collaborated with 7 pathologists, but I am not an expert pathologist. 8 Q. And would you agree do that not have 9 expertise in pathology? 10 MS. PARFITT: Objection. Asked and 11 answered. 12 THE WITNESS: You asked that I -- I do 13 not have expertise in pathology. I stated that I am 14 not a pathologist, but I do know some pathology from 15 my work in ovarian cancer and other cancers over the 16 years. So to say that I have no expertise isn't -- 17 I don't think that is correct. But we both -- I 18 acknowledge that I am not a trained pathologist. 19 BY MR. JAMES: 20 Q. Do you recall being asked in Ingham if you 21 considered yourself to have expertise in pathology? 22 A. I don't recall that question, specifically. 23 Q. I'm going to hand you a copy of the 24 transcript from Ingham that I brought with me, and I'm 25 going to refer you --</p>	<p>1 BY MR. JAMES: 2 Q. Have you done anything between your March 3 deposition and today in regards to obtaining expertise 4 in pathology? 5 A. No, I have not. 6 Q. Dr. Moorman, that's all I have on the 7 transcript for right now. 8 Dr. Moorman, do you agree that, prior to 9 offering expert opinion on a particular topic, an 10 expert should be conducted to -- expected to conduct a 11 comprehensive review of the medical and scientific 12 literature on that topic? 13 A. I'm sorry, I'm reading the question. 14 I -- I think that it is important to be 15 comprehensive. I think it's also important to 16 recognize that there are expertise in different areas. 17 And so we recognize that my expertise is in 18 epidemiology, and I have supplemented that with 19 other -- information from other areas as well. 20 Q. And with respect to the epidemiology on talc 21 and ovarian cancer, do you believe you conducted a 22 comprehensive review of that body of literature? 23 A. I believe that I have. 24 Q. Do you believe you conducted a comprehensive 25 review of the literature and scientific evidence on</p>
Page 55	Page 57
<p>1 MR. JAMES: And, Ms. Parfitt, I have 2 two copies, unfortunately, not three. And this will 3 be just a couple questions, Ms. Parfitt. So if you 4 bear with me -- 5 MS. PARFITT: You can just direct me to 6 the page. 7 MR. JAMES: Sure. Looking at page 280. 8 MS. PARFITT: Just bear with us both -- 9 me. All right. 10 MR. JAMES: I'm looking at lines 12 11 through 14. 12 MS. PARFITT: Thank you. 13 BY MR. JAMES: 14 Q. Do you see the question, Dr. Moorman, where 15 you were asked if you have expertise in pathology? 16 Do you see that question? 17 A. I do. 18 Q. Okay. And you answered that you do not; 19 correct? 20 MS. PARFITT: Objection. 21 THE WITNESS: Yes, that is how 22 I answered. I think that the more qualified answer 23 that I gave today is probably a more accurate 24 representation. 25</p>	<p>1 mechanism? 2 A. I considered the scientific mechanisms and, 3 again, recognizing what my expertise is. As I have 4 indicated earlier, I am not a cancer biologist. I'm 5 not a laboratory scientist. I consider some of that 6 data, but I recognize that I am not -- you know, that 7 is not my major area of expertise. 8 Q. And I do understand from your MDL report that 9 you considered biology; correct? 10 A. I did consider biology. 11 Q. And so my precise question is whether you 12 conducted a comprehensive review on the issue of 13 mechanism. 14 MS. PARFITT: Objection. Asked and 15 answered. 16 THE WITNESS: I considered it, and, 17 again, I think that there is information out there 18 that a cancer biologist would have the expertise to 19 review it in more detail because of their training, 20 which is different than the training and expertise 21 that I have. 22 MR. JAMES: I object to the 23 nonresponsive portion of the answer. 24 BY MR. JAMES: 25 Q. Dr. Moorman, did you conduct a comprehensive</p>

15 (Pages 54 to 57)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 58	Page 60
<p>1 review of all of the literature on animal studies and 2 talc? 3 MS. PARFITT: Objection. Form. 4 THE WITNESS: I don't believe that -- I 5 cannot say that I considered -- identified or 6 considered every animal study. 7 MR. JAMES: Object to the nonresponsive 8 answer. 9 BY MR. JAMES: 10 Q. Did you conduct a comprehensive review of the 11 literature on animal studies and talc? 12 MS. PARFITT: Asked and answered. 13 Objection. 14 THE WITNESS: I -- I believe that 15 I answered your question. I said that I don't think 16 that I identified or considered every animal study 17 related to talc and ovarian cancer. 18 BY MR. JAMES: 19 Q. Did you conduct a comprehensive review of 20 cell studies and talc? 21 A. Once again, I considered some of that 22 literature. Whether it was comprehensive or not, I -- 23 I don't think that I have the expertise to say that 24 I considered all of the cell studies and talc. 25 Q. Did you conduct a comprehensive review on the</p>	<p>1 have referred to another article. 2 Q. Did you conduct a comprehensive review of the 3 genotoxicity studies that are relevant to talc and 4 ovarian cancer? 5 A. My answer to this question is similar to the 6 answers that I have given there. 7 I have read some of the mechanistic studies. 8 I would not say that I necessarily identified every 9 relevant genotoxicity study. 10 Q. And I'm not asking you, Dr. Moorman, if you 11 did find 100 percent of the studies. I'm asking you 12 if part of your review in this case began with the 13 intention to capture that body of literature. 14 MS. PARFITT: Objection. Asked and 15 answered several times. 16 THE WITNESS: My intent was, as an 17 epidemiologist, was to be very comprehensive in my 18 area of expertise. There were certainly some other 19 related areas where I reviewed the literature, but 20 there are experts that will speak to that more 21 directly because of their expertise. 22 BY MR. JAMES: 23 Q. Okay. So will you agree with me today that 24 you have not conducted a comprehensive review of the 25 cell studies and talc?</p>
Page 59	Page 61
<p>1 issue of migration in this case? 2 A. I believe -- again, I considered every study 3 that I was aware of on migration of talc. It's a 4 little bit outside my area of expertise, so I am not 5 sure that I identified every single study in that 6 regard. 7 Q. And with the methods that you applied in this 8 case, was it your intention to capture every study 9 pertaining to the issue of migration? 10 MS. PARFITT: Objection. Form. 11 THE WITNESS: I tried -- you know, my 12 intent was to read the articles that I was aware of, 13 that were brought to my attention. Because it is a 14 little bit outside my area of expertise, I cannot say 15 with 100 percent certainty that I identified every 16 single study related to migration. 17 BY MR. JAMES: 18 Q. But you testified that your intent was to 19 read the articles that you are aware of or that were 20 brought to your attention. 21 When you say brought to your attention, was 22 that by Plaintiffs' counsel? 23 A. It's some -- some of them could have been 24 brought to my attention in that way. Some of them 25 could have been -- like, an article that I read might</p>	<p>1 MS. PARFITT: Objection. Misstates her 2 testimony. 3 You may answer, Dr. Moorman. 4 THE WITNESS: I -- I think that -- 5 I think that it is fair to say that I have probably 6 not reviewed every cell study and talc. 7 BY MR. JAMES: 8 Q. Okay. Dr. Moorman, I'm going to refer you 9 back to the Ingham transcript, please, that's in front 10 of you. 11 MS. PARFITT: Are we marking this, 12 Scott? 13 MR. JAMES: We can. Sure. 14 Dr. Moorman, when we finish this, I'll take 15 that back from you and mark it as Exhibit No. 11. 16 Okay? 17 (Exhibit No. 11 was marked for identification.) 18 BY MR. JAMES: 19 Q. Dr. Moorman, if you look at page 35 of your 20 transcript, please. And if you look at lines -- it's 21 lines 11 through 17. It's a question and answer. If 22 you could review that for me. 23 A. Okay. 24 Q. And do you see that on line 16, you answered 25 in Ingham:</p>

16 (Pages 58 to 61)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 62	Page 64
<p>1 "I have not done a comprehensive 2 review of those studies." 3 And there, you're referring to cell studies; 4 correct? 5 A. Yes, that is what it says here. 6 Q. Is that a truthful answer? 7 A. I think -- 8 MS. PARFITT: Objection. Form. 9 Go ahead. 10 THE WITNESS: I think that we -- you 11 know, as you have asked me the questions and I have 12 responded to them, that it's -- I have looked at some 13 of these studies. I would not have looked at all of 14 them. 15 BY MR. JAMES: 16 Q. As an epidemiologist, do you understand the 17 significance of the term "comprehensive review"? 18 A. Yes, I understand the term. 19 Q. Okay. And you understand that you have 20 testified that you conducted a comprehensive review of 21 the epidemiology literature for talc and ovarian 22 cancer; correct? 23 MS. PARFITT: Asked and answered. 24 THE WITNESS: Yes. 25</p>	<p>1 literature in greater detail. 2 Q. Have you undertaken a comprehensive review of 3 literature pertaining to the allegation that asbestos 4 may contaminate talcum powder products? 5 MS. PARFITT: Objection. Form. 6 THE WITNESS: A comprehensive review of 7 the literature pertaining to the allegation that 8 asbestos may contaminate talcum powder? 9 I have read quite a few articles and 10 documents addressing that. Whether or not I have read 11 every document addressing that, I'm not absolutely 12 sure. 13 BY MR. JAMES: 14 Q. Okay. Dr. Moorman, you're answering a 15 question that I didn't ask. And so I object to the 16 nonresponsiveness again. 17 Did you conduct a comprehensive review of 18 the body of literature assessing whether asbestos 19 contaminates talcum powder products? 20 A. I believe that I have answered your question. 21 It's -- 22 Q. Could you please answer it again. 23 A. I have read many articles on it. I do not 24 know that I have read every article related to that 25 topic, again. So...</p>
Page 63	Page 65
<p>1 BY MR. JAMES: 2 Q. And so I'm asking if you have applied the 3 same comprehensive review to these other areas, 4 including cell studies, animal studies, and mechanism 5 studies. 6 MS. PARFITT: Objection. Form. Asked 7 and answered. 8 BY MR. JAMES: 9 Q. Have you conducted the same comprehensive 10 review on that body of literature that you've 11 conducted on the epidemiology? 12 MS. PARFITT: Objection. 13 THE WITNESS: Once again, I have 14 answered the question. This is not my primary area of 15 expertise. And so I have not done the review to the 16 depth and the -- as comprehensive as I have done in my 17 area of expertise, which is epidemiology. 18 BY MR. JAMES: 19 Q. Have you done a comprehensive review of the 20 epidemiology on the relationship between asbestos and 21 ovarian cancer? 22 A. I believe that I have looked at a pretty 23 comprehensive -- I've had a pretty comprehensive look 24 at the asbestos and ovarian cancer. I believe that 25 I have looked at the talcum -- talc and ovarian cancer</p>	<p>1 Q. You understand that if you were going to 2 publish an opinion in peer-reviewed literature about 3 the allegation that asbestos contaminates talcum 4 powder products, you would be expected to conduct a 5 comprehensive review of that literature; correct? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: If I were to publish an 8 opinion in a peer-reviewed literature, you would want 9 to have a comprehensive review of the literature, yes. 10 BY MR. JAMES: 11 Q. And have you conducted a comprehensive review 12 of the literature on that topic, such that you would 13 feel comfortable providing an opinion for a 14 peer-reviewed journal? 15 MS. PARFITT: Objection. Form. 16 BY MR. JAMES: 17 Q. And the topic being the allegation that 18 asbestos contaminates talcum powder products. 19 MS. PARFITT: Objection. Form. 20 THE WITNESS: I think that I'm maybe 21 having some difficulty answering this question because 22 it would seem like this would be a topic that would be 23 more appropriately addressed by a mineralogist. And 24 I -- I actually cannot see myself writing a 25 peer-reviewed article about this because it seems</p>

17 (Pages 62 to 65)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 66</p> <p>1 somewhat -- it's related to the epidemiology of talc 2 and ovarian cancer, but I would not be writing an 3 article focused solely on that. 4 BY MR. JAMES: 5 Q. You understand that, in your expert report, 6 you have opined with -- that there's "credible 7 evidence" there has been asbestos in talcum power 8 products. 9 Do you recall making that conclusion in your 10 report? 11 A. Yes. 12 Q. So to support that conclusion that you 13 believe there's "credible evidence" in talcum powder 14 products, did you conduct a systematic review of the 15 literature to support that conclusion? 16 A. I did not -- 17 MS. PARFITT: I'm going to object to 18 the form of the question. Some words were left out. 19 You may answer. 20 THE WITNESS: In my report, I cited 21 literature that did support that opinion. 22 Did I conduct a systematic review that 23 identified possibly every piece of literature that 24 addressed the topic? No, I did not do that. 25</p>	<p style="text-align: right;">Page 68</p> <p>1 A. It was part of the basis for my opinion, 2 along with some peer-reviewed literature. 3 Q. Okay. With respect to the company documents, 4 were those documents hand-selected for you by 5 Plaintiffs' counsel? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: They were provided to me 8 by Plaintiffs' counsel. 9 BY MR. JAMES: 10 Q. Okay. When you saw those documents, did you 11 ask if there were additional documents that would 12 address the issue of asbestos contamination? 13 A. I don't know that I asked if there were 14 additional documents. It was my impression that there 15 were probably many other documents related to this 16 that were not provided to me. 17 Q. And as a scientist, wouldn't you be 18 interested in knowing if there are other documents 19 that have been produced in this litigation that rebut 20 the claim that asbestos contaminates talcum powder 21 products? 22 MS. PARFITT: Objection. Form. 23 THE WITNESS: This is an interesting 24 question because the claim had been made that 25 asbestos -- or, rather, that talcum -- talcum powder</p>
<p style="text-align: right;">Page 67</p> <p>1 BY MR. JAMES: 2 Q. Do you believe that the standards for 3 providing opinions in litigation reports differ from 4 the standards for providing opinions in published 5 literature? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: No. No. I think that 8 one is trying to provide evidence to support one's 9 opinions. 10 BY MR. JAMES: 11 Q. With respect to the issue of asbestos 12 contamination, Dr. Moorman, you said you did review 13 some articles. 14 How did you characterize that? 15 A. I said that I reviewed some -- some articles 16 and some -- some documents. I don't think that 17 I reviewed every article or document that is available 18 on that topic. 19 Q. With respect to documents, are you referring 20 to company documents provided to you by Plaintiffs' 21 counsel? 22 A. That -- that's part of what I reviewed, some 23 of those documents provided by counsel. 24 Q. And looking at those documents provided the 25 basis for your opinion; is that right?</p>	<p style="text-align: right;">Page 69</p> <p>1 products had been asbestos-free since 1976. And it 2 is -- the documents provided, including the 3 peer-reviewed as well as the other, saying that -- 4 provide evidence that that is not an accurate 5 statement. 6 We're not saying that every container of 7 talcum powder contains asbestos, but what I was saying 8 in my report is that there is evidence that some 9 talcum powder products have asbestos in them. 10 MR. DONATH: Move to strike, 11 nonresponsive. 12 BY MR. JAMES: 13 Q. So are you changing your report -- because in 14 the report, you say that there is "credible evidence." 15 Do you recall making that conclusion? 16 A. Yes. 17 Q. As a scientist, you understand that to give 18 something credit, you would necessarily need to 19 consider both sides of the story; correct? 20 MS. PARFITT: Objection. Misstates her 21 testimony. She's... 22 You can answer, Dr. Moorman. 23 THE WITNESS: I'm sorry? 24 MS. PARFITT: I said it misstates what 25 you're trying to suggest to the ladies and gentlemen</p>

18 (Pages 66 to 69)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 70	Page 72
<p>1 of the jury.</p> <p>2 But if you can answer that question again,</p> <p>3 please try and answer Mr. James' question. And</p> <p>4 look -- if you need to look at the question, please</p> <p>5 do.</p> <p>6 THE WITNESS: I think that I did -- it</p> <p>7 says "As a scientist, you understand that to give</p> <p>8 something credit, you would necessarily need to</p> <p>9 consider both sides of the story."</p> <p>10 And I think that I did consider both sides</p> <p>11 of the story.</p> <p>12 I think that, as I stated, the evidence does</p> <p>13 not suggest that every container of talcum powder has</p> <p>14 detectable asbestos in it. But my statement that</p> <p>15 there is credible evidence that some talcum powder</p> <p>16 products contain asbestos, I think that that statement</p> <p>17 is absolutely true. There is some evidence to</p> <p>18 indicate that some talcum powder -- or asbestos has</p> <p>19 been identified in some talcum powder products.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. Do you understand what Johnson & Johnson's</p> <p>22 position is with respect to that claim?</p> <p>23 A. I -- I don't know specifically. Perhaps you</p> <p>24 could -- could tell me.</p> <p>25 Q. You understand that Johnson & Johnson's</p>	<p>1 company documents and other materials to support your</p> <p>2 conclusions about asbestos contamination?</p> <p>3 A. I -- I wouldn't be able to quantify that.</p> <p>4 I don't know specifically.</p> <p>5 Q. Can you give us an estimate?</p> <p>6 A. I think it would be pretty difficult to come</p> <p>7 up with an estimate. You know, I read some documents</p> <p>8 from the company. I read documents -- some</p> <p>9 peer-reviewed literature. I reviewed documents</p> <p>10 provided by Plaintiffs' counsel.</p> <p>11 Perhaps -- I don't know. Perhaps ten -- ten</p> <p>12 hours or so.</p> <p>13 Q. When you said that you reviewed company</p> <p>14 documents, again, those are the documents provided to</p> <p>15 you by Plaintiffs' counsel; correct?</p> <p>16 A. Yes.</p> <p>17 MS. PARFITT: Objection. Form.</p> <p>18 THE WITNESS: Yes, the Plaintiff</p> <p>19 provided those documents to me.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. And you did not ask Plaintiffs' counsel to</p> <p>22 provide you additional documents once you saw the</p> <p>23 first batch of documents; correct?</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25 THE WITNESS: I did not ask, no.</p>
Page 71	Page 73
<p>1 position is that talcum powder products have not been</p> <p>2 contaminated with asbestos? Do you know that that's</p> <p>3 Johnson & Johnson's position?</p> <p>4 A. I -- if you are telling me that now, I don't</p> <p>5 know that I have -- I -- I'm trying to think what</p> <p>6 I have read. I think that, yes, I have probably read</p> <p>7 statements from the company that describes that as</p> <p>8 their position.</p> <p>9 Q. And do you know what Johnson & Johnson bases</p> <p>10 their position on?</p> <p>11 A. Not specifically.</p> <p>12 Q. Wouldn't that be pretty important to</p> <p>13 understand before making an opinion about whether</p> <p>14 there's credible evidence of asbestos contamination?</p> <p>15 MS. PARFITT: Objection. Form.</p> <p>16 THE WITNESS: Again, I think that when</p> <p>17 one is trying to make a statement that there is no</p> <p>18 asbestos contained in talc products, if you are</p> <p>19 finding evidence from multiple sources that there is</p> <p>20 asbestos contained in some talc products, that</p> <p>21 supports the statement that I made in report that</p> <p>22 there is credible evidence that not all talc products</p> <p>23 are asbestos-free.</p> <p>24 BY MR. JAMES:</p> <p>25 Q. How many hours did you spend reviewing</p>	<p>1 BY MR. JAMES:</p> <p>2 Q. You also looked at litigation reports from</p> <p>3 Plaintiffs' expert regarding asbestos contamination;</p> <p>4 correct?</p> <p>5 A. Yes, I did.</p> <p>6 Q. And you understand those experts are paid</p> <p>7 litigation experts by the Plaintiffs; correct?</p> <p>8 MS. PARFITT: Objection. Form.</p> <p>9 THE WITNESS: Yes, I understand that</p> <p>10 they are paid by the Plaintiffs.</p> <p>11 BY MR. JAMES:</p> <p>12 Q. One of those experts is Longo; correct?</p> <p>13 A. That is correct.</p> <p>14 MS. PARFITT: Is that Dr. Longo?</p> <p>15 MR. JAMES: Thank you, Michelle.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. Dr. Longo; is that correct?</p> <p>18 A. That is correct.</p> <p>19 Q. Okay. So you reviewed Dr. Longo's reports?</p> <p>20 A. I looked at them, yes.</p> <p>21 Q. Okay. Do you understand that in this</p> <p>22 litigation, Johnson & Johnson has presented experts to</p> <p>23 rebut Dr. Longo's findings?</p> <p>24 MS. PARFITT: Objection. Just let the</p> <p>25 record reflect that the defense expert reports have</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 74	Page 76
<p>1 not yet been provided in this litigation, in the MDL</p> <p>2 litigation, so it would have been difficult to provide</p> <p>3 that to Dr. Moorman.</p> <p>4 BY MR. JAMES:</p> <p>5 Q. You can still answer the question.</p> <p>6 A. It would not surprise me to know that there</p> <p>7 were reports provided by -- that was done for the</p> <p>8 defense, but I have not seen them.</p> <p>9 Q. Did you ask to see them?</p> <p>10 MS. PARFITT: Objection. Form.</p> <p>11 THE WITNESS: I did not ask to see --</p> <p>12 no, I did not.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. And counsel just made a note on the record</p> <p>15 about these litigation reports from the defense not</p> <p>16 being made available yet in the MDL.</p> <p>17 Do you understand that the defense has</p> <p>18 presented experts, for example, in the Ingham case to</p> <p>19 rebut Dr. Longo's findings?</p> <p>20 A. I was not specifically aware of that. It</p> <p>21 would not surprise me, however.</p> <p>22 Q. You understand Dr. Longo's litigation reports</p> <p>23 that you reviewed, those are not peer-reviewed.</p> <p>24 Do you understand that?</p> <p>25 MS. PARFITT: Objection. Form.</p>	<p>1 there's no safe level of asbestos, that any level of</p> <p>2 asbestos in a talcum powder product is bad for the</p> <p>3 health of the people who use it.</p> <p>4 Q. Do you intend to offer any opinions about the</p> <p>5 purported amount of contamination in talcum powder</p> <p>6 products over the course of history?</p> <p>7 MS. PARFITT: Objection. Form.</p> <p>8 THE WITNESS: I am not going to offer</p> <p>9 an opinion about the quantity of asbestos in talcum</p> <p>10 powder products.</p> <p>11 BY MR. JAMES:</p> <p>12 Q. Have you, in the course of forming your</p> <p>13 opinions in this case, ever reviewed the FDA testing</p> <p>14 of talcum powder products for the presence of</p> <p>15 asbestos?</p> <p>16 A. I recall reviewing a document from FDA, yes.</p> <p>17 Q. Okay. And that document is not discussed in</p> <p>18 your report, is it?</p> <p>19 A. No, I don't think that I specifically</p> <p>20 reference that.</p> <p>21 Q. Why is that?</p> <p>22 A. I don't -- I don't know why I didn't</p> <p>23 reference it. I read it, but...</p> <p>24 MR. JAMES: I'm marking Exhibit No. 11</p> <p>25 [sic], talc testing information from the FDA, that I'm</p>
Page 75	Page 77
<p>1 THE WITNESS: Yes, I know that they are</p> <p>2 not peer-reviewed.</p> <p>3 BY MR. JAMES:</p> <p>4 Q. With regard to the literature that you've</p> <p>5 referenced having reviewed pertaining to the</p> <p>6 allegation that talcum powder products are</p> <p>7 contaminated with asbestos, what does that literature</p> <p>8 say about Johnson & Johnson products specifically?</p> <p>9 A. I'm trying to recall specifically. I believe</p> <p>10 that some of the articles were not specific about the</p> <p>11 particular brand names that they tested. I think they</p> <p>12 just described them as commercially available</p> <p>13 products. But I believe that -- I want to say that</p> <p>14 I recall at least one that described the products as</p> <p>15 being Johnson & Johnson.</p> <p>16 Q. With respect to everything that you reviewed</p> <p>17 pertaining to your claim in your report of "credible</p> <p>18 evidence" of contamination of talcum powder products,</p> <p>19 what did everything you reviewed tell us about the</p> <p>20 amount of contamination in the products?</p> <p>21 Do you have any opinions about amount?</p> <p>22 A. I do. My opinions are that most of the</p> <p>23 analyses that detected asbestos fibers in talcum</p> <p>24 powder products detected low levels, and putting that</p> <p>25 in the context that asbestos has been characterized as</p>	<p>1 handing you, Dr. Moorman.</p> <p>2 (Exhibit No. 12 was marked for identification.)</p> <p>3 MR. JAMES: I provided an extra copy if</p> <p>4 you want to hand one to your counsel, please. Thank</p> <p>5 you much.</p> <p>6 MR. FARIES: This is 12.</p> <p>7 MS. PARFITT: 11 is the transcript.</p> <p>8 MR. JAMES: Got it. Thank you. I'll</p> <p>9 fix the sticker once we finish the question.</p> <p>10 MS. PARFITT: No worries.</p> <p>11 BY MR. JAMES:</p> <p>12 Q. Okay. Dr. Moorman, is this the document that</p> <p>13 you had seen before?</p> <p>14 A. I'm not sure if this is the same one or if</p> <p>15 I -- no, I -- actually, I think that I did see this.</p> <p>16 Q. And if you look over on page 2 of the</p> <p>17 exhibit -- it's page 2 of 8 -- do you see at the</p> <p>18 bottom, it says in the section "The results of FDA's</p> <p>19 survey" -- do you see where I'm reading?</p> <p>20 A. Yes.</p> <p>21 Q. And the FDA here says (as read):</p> <p>22 "The survey found no asbestos</p> <p>23 fibers or structures in any of the</p> <p>24 samples of cosmetic-grade raw</p> <p>25 material talc or cosmetic products</p>

20 (Pages 74 to 77)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 78	Page 80
<p>1 containing talc." 2 Did I read that correctly? 3 A. You did. 4 MS. PARFITT: Are you going to complete 5 this paragraph, or are you going to leave it at that? 6 MR. JAMES: Michelle, you'll have an 7 opportunity to ask your questions. 8 MS. PARFITT: Well, just for 9 completeness. Certainly, if that's how you'd like to 10 handle it, that's fine. 11 MR. JAMES: Okay. That's how it works. 12 MS. PARFITT: Oh, I -- Scott, you don't 13 have to educate me on how it works. I get how you're 14 working, and we'll make it work on our side too. 15 Thank you. 16 BY MR. JAMES: 17 Q. Dr. Moorman, is that conclusion cited 18 anywhere in your report? 19 A. That -- 20 MS. PARFITT: Objection to the partial 21 conclusion. 22 Please answer. 23 THE WITNESS: Right. It's -- I did not 24 put it in there. However, I considered as I was, you 25 know, evaluating this literature, what it goes on to</p>	<p>1 proportion of the talcum powder products in the US are 2 Johnson & Johnson products. 3 Q. Do you know if the FDA test results 4 specifically pertain to Johnson & Johnson products? 5 A. I'm -- I believe that some of the products 6 tested -- I believe that some of them were Johnson & 7 Johnson products, if I'm not mistaken. But I can't 8 say that with certainty. 9 Actually, when I look at the report, I do 10 see that they list Johnson's baby powder. 11 Q. And, Dr. Moorman, you're referring to page 7; 12 correct? 13 A. Yes. 14 Q. Okay. Do you understand that the FDA also 15 tested samples provided to them by the supplier of 16 talc for Johnson & Johnson products? Did you know 17 that? 18 A. I -- I think that I knew that. I believe 19 I did know that. 20 Q. Again, that's not quoted anywhere in your 21 report either, is it? 22 A. No, that is -- 23 MS. PARFITT: Object to form. 24 THE WITNESS: -- not. 25</p>
Page 79	Page 81
<p>1 say (as read): 2 "The results were limited by the 3 fact that only four talc suppliers 4 submitted samples and by the 5 number of products tested." 6 BY MR. JAMES: 7 Q. Okay. 8 A. And so it goes on to say, you know, 9 (as read): 10 "They do not prove that most or 11 all talc or talc-containing 12 cosmetic products currently 13 marketed in the US are likely to 14 be free of asbestos 15 contamination." 16 So... 17 Q. You're offering opinions in the MDL -- let me 18 re-ask this. 19 Are you offering opinions in the MDL that 20 Johnson & Johnson talcum powder products have been 21 contaminated with asbestos at some point in time? 22 A. In my opinion, I am referring to talcum 23 powder products. Okay? I don't believe in my report, 24 I ever specifically say Johnson & Johnson talcum 25 powder products, but I do recognize that a large</p>	<p>1 BY MR. JAMES: 2 Q. Before offering opinions about "credible 3 evidence," don't you think it would be important to 4 mention the findings of the FDA on such an important 5 issue? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: As I have stated before, 8 my opinion was that there is credible evidence that -- 9 from peer-reviewed articles, from some other sources 10 as well, that asbestos has been found in talcum powder 11 products. I believe that that evidence is credible. 12 I did not make the statement that it is in 13 all products, but I think that my statement that there 14 is credible evidence that some talcum powder products 15 contain asbestos I think is accurate. 16 BY MR. JAMES: 17 Q. And is that a conclusion that you would feel 18 comfortable providing in published peer-reviewed 19 literature? 20 MS. PARFITT: Objection. Form. 21 THE WITNESS: To say that there is 22 credible evidence that some talcum powder products 23 contain asbestos, I think that that -- I would feel 24 comfortable saying that based on peer-reviewed 25 literature that has found that.</p>

21 (Pages 78 to 81)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 82	Page 84
<p>1 BY MR. JAMES:</p> <p>2 Q. But you never undertook an effort to conduct</p> <p>3 a comprehensive review of the literature on the topic,</p> <p>4 did you?</p> <p>5 MS. PARFITT: Objection. Form. Asked</p> <p>6 and answered several times.</p> <p>7 THE WITNESS: Yes, I feel like I -- you</p> <p>8 have asked that, and I think that I have answered it.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. What's your answer?</p> <p>11 A. My answer is that I have found evidence</p> <p>12 that -- from peer-reviewed literature, from other</p> <p>13 documents, that some asbestos has been detected in</p> <p>14 some talcum powder products.</p> <p>15 Q. With regard to the company documents that you</p> <p>16 reviewed that were provided to you by Plaintiffs'</p> <p>17 counsel, do you consider yourself an expert in</p> <p>18 reviewing the information conveyed by those documents?</p> <p>19 MS. PARFITT: Objection. Form.</p> <p>20 THE WITNESS: As I have indicated</p> <p>21 previously, I am not a mineralogist or a geologist,</p> <p>22 and so I would not consider myself an expert in</p> <p>23 reviewing those types of documents.</p> <p>24 BY MR. JAMES:</p> <p>25 Q. Do you have any knowledge about the</p>	<p>1 BY MR. JAMES:</p> <p>2 Q. Dr. Moorman, have you seen a 2014 letter from</p> <p>3 the FDA addressing a request for a warning on talcum</p> <p>4 powder products?</p> <p>5 A. Yes, I have.</p> <p>6 Q. Do you know that within that letter, the FDA</p> <p>7 comments on the issue of alleged asbestos</p> <p>8 contamination?</p> <p>9 MS. PARFITT: Objection. Form.</p> <p>10 THE WITNESS: If I could see the</p> <p>11 document. It has been a while since I have actually</p> <p>12 looked at it.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. Absolutely.</p> <p>15 MR. JAMES: And if counsel could remind</p> <p>16 me, are we now on 13?</p> <p>17 MS. PARFITT: We are indeed.</p> <p>18 MR. JAMES: Thank you.</p> <p>19 MS. PARFITT: You are very welcome.</p> <p>20 (Exhibit No. 13 was marked for identification.)</p> <p>21 BY MR. JAMES:</p> <p>22 Q. Okay. Dr. Moorman, I'm handing you a copy of</p> <p>23 the 2014 FDA letter with an extra copy to pass to your</p> <p>24 counsel.</p> <p>25 MS. PARFITT: Thank you.</p>
Page 83	Page 85
<p>1 specifications that are used by Johnson & Johnson in</p> <p>2 manufacturing its talcum powder products?</p> <p>3 A. No, I do not.</p> <p>4 Q. Do you have any expertise in the sufficiency</p> <p>5 of the specifications to detect the presence of</p> <p>6 asbestos?</p> <p>7 A. No, I do not.</p> <p>8 Q. Did you know that Johnson & Johnson produces</p> <p>9 its talcum powder products in accordance with</p> <p>10 specifications set out by the US Pharmacopeial</p> <p>11 Convention?</p> <p>12 MS. PARFITT: Objection. Form.</p> <p>13 THE WITNESS: I was not specifically</p> <p>14 aware of that. I don't know what their specifications</p> <p>15 are.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. Did Plaintiffs' counsel provide to you those</p> <p>18 specifications?</p> <p>19 A. Not that I recall.</p> <p>20 Q. Did you know that the specifications provide</p> <p>21 mechanisms to test for the absence of asbestos?</p> <p>22 MS. PARFITT: Objection. Form.</p> <p>23 THE WITNESS: I have already stated</p> <p>24 that I -- I don't know what those specifications are.</p> <p>25</p>	<p>1 BY MR. JAMES:</p> <p>2 Q. Dr. Moorman, if you could turn to the second</p> <p>3 page of the letter. Is this the letter that you've</p> <p>4 seen before, Dr. Moorman?</p> <p>5 A. Yes, it is.</p> <p>6 Q. And do you see that, in the section entitled</p> <p>7 "Chemistry Findings," there's a discussion there by</p> <p>8 the FDA pertaining to asbestos; correct?</p> <p>9 A. Yes, I see that.</p> <p>10 Q. And do you see that at the bottom of the</p> <p>11 letter, the very last sentence, the FDA says</p> <p>12 (as read):</p> <p>13 "You have not provided evidence</p> <p>14 that asbestos-contaminated</p> <p>15 talc-containing cosmetic products</p> <p>16 are currently being marketed,</p> <p>17 since the data submitted is almost</p> <p>18 40 years old."</p> <p>19 Do you see that?</p> <p>20 A. I do see that.</p> <p>21 Q. Okay. And you said that you have reviewed</p> <p>22 this letter in its entirety before?</p> <p>23 A. I have read it, yes.</p> <p>24 Q. Do you have any reason to quarrel with the</p> <p>25 scientists at the FDA that have looked at the issue of</p>

22 (Pages 82 to 85)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 86</p> <p>1 asbestos contamination in talcum powder products?</p> <p>2 MS. PARFITT: Objection. Form.</p> <p>3 THE WITNESS: I don't know who those</p> <p>4 scientists are. I don't know any scientists at the</p> <p>5 FDA who would have done -- would have done this. I --</p> <p>6 so I can't say that I have a quarrel with them because</p> <p>7 I don't know them.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. Do you have any opinions about the type of</p> <p>10 asbestos that is alleged to contaminate talcum powder</p> <p>11 products?</p> <p>12 A. I am certainly aware that there are different</p> <p>13 types of asbestos. Again, from a health perspective,</p> <p>14 there is no safe form of asbestos. So if there are</p> <p>15 different types, it really doesn't make a lot of</p> <p>16 difference in terms of the potential health effects.</p> <p>17 MR. JAMES: Object to the nonresponsive</p> <p>18 portion.</p> <p>19 BY MR. JAMES:</p> <p>20 Q. Do you intend to offer any opinions about the</p> <p>21 type of asbestos that Plaintiffs contend contaminates</p> <p>22 talcum powder products?</p> <p>23 A. No, I am not going to specifically address</p> <p>24 the types of asbestos in talcum powder products.</p> <p>25 Q. Do you hold the opinion that asbestos causes</p>	<p style="text-align: right;">Page 88</p> <p>1 Did you form your opinions about asbestos</p> <p>2 and talcum powder that are contained within your MDL</p> <p>3 report after being retained as an expert?</p> <p>4 MS. PARFITT: Object to form.</p> <p>5 THE WITNESS: I -- it is often -- has</p> <p>6 often been reported in the literature that talcum</p> <p>7 powder contained asbestos prior to 1976, and that</p> <p>8 products produced after that did not contain asbestos.</p> <p>9 And as I became involved in this litigation,</p> <p>10 I was made aware of and discovered some of the</p> <p>11 articles that showed that talcum powder products after</p> <p>12 1976 contained asbestos.</p> <p>13 And so my opinion was that -- my opinion</p> <p>14 that asbestos in current or recently marketed talcum</p> <p>15 powder products could explain -- was part of the</p> <p>16 biological mechanism by which exposure to talcum</p> <p>17 powder, that was -- that was formed as I became aware</p> <p>18 of more of the available information, when I became</p> <p>19 involved in this litigation.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. Setting aside the issue of asbestos in talcum</p> <p>22 powder, do you believe that asbestos is a cause of</p> <p>23 ovarian cancer?</p> <p>24 A. Yes, I do.</p> <p>25 Q. How many studies have explored the link</p>
<p style="text-align: right;">Page 87</p> <p>1 ovarian cancer?</p> <p>2 A. Yes.</p> <p>3 Q. Do you hold the opinion that exposure to</p> <p>4 asbestos through use of talcum powder products causes</p> <p>5 ovarian cancer?</p> <p>6 A. My opinion is based on exposure to talcum</p> <p>7 powder products and whatever is contained within them.</p> <p>8 And so if there is asbestos within talcum powder</p> <p>9 products, which we have some evidence to suggest that</p> <p>10 that is the case, then that provides a potential</p> <p>11 biological mechanism by which talcum powder products</p> <p>12 could cause ovarian cancer.</p> <p>13 Q. The opinion that you have pertaining to</p> <p>14 asbestos and ovarian cancer, did you form that opinion</p> <p>15 in the context of litigation?</p> <p>16 MS. PARFITT: Objection. Form.</p> <p>17 THE WITNESS: I'm not sure how -- could</p> <p>18 you perhaps restate the question?</p> <p>19 BY MR. JAMES:</p> <p>20 Q. Absolutely.</p> <p>21 A. I'm not sure --</p> <p>22 Q. Absolutely.</p> <p>23 A. -- what you're asking.</p> <p>24 Q. Did you form the opinion that -- did you</p> <p>25 form -- let me start over.</p>	<p style="text-align: right;">Page 89</p> <p>1 between asbestos and ovarian cancer?</p> <p>2 MS. PARFITT: Objection. Form.</p> <p>3 THE WITNESS: In terms of epidemiologic</p> <p>4 literature, there have been a couple of meta-analyses;</p> <p>5 and the exact number, I don't have that off the top of</p> <p>6 my head, but I want to say approximately a dozen</p> <p>7 studies.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. Did you review the entire body of literature</p> <p>10 looking at a purported link between asbestos and</p> <p>11 ovarian cancer?</p> <p>12 MS. PARFITT: Objection. Form.</p> <p>13 THE WITNESS: I know that I looked at</p> <p>14 the meta-analyses. I looked at some data from IARC,</p> <p>15 and I believe that I have looked in some degree at,</p> <p>16 I think, all of the epidemiologic studies about</p> <p>17 asbestos and ovarian cancer.</p> <p>18 BY MR. JAMES:</p> <p>19 Q. So did you look at all of the studies that</p> <p>20 are discussed in the IARC monograph?</p> <p>21 MS. PARFITT: Objection. Form.</p> <p>22 THE WITNESS: I have -- the IARC</p> <p>23 monograph, as they typically do, they look at many of</p> <p>24 the animal studies, some of the laboratory studies.</p> <p>25 I have not looked at all of them. I have looked at</p>

23 (Pages 86 to 89)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 90	Page 92
<p>1 the epidemiologic studies, which, again, is my area of 2 expertise. 3 BY MR. JAMES: 4 Q. And we're speaking currently about the IARC 5 monograph on asbestos; correct? 6 A. Correct. 7 Q. On page 34 of your report, if that you have 8 handy, Dr. Moorman -- actually, I think I have the 9 wrong page number. Give me one second. 10 Okay. It's actually page 35. My apologies. 11 And you see -- I'm looking at the first -- 12 the top paragraph. And you state in the second 13 sentence -- do you see where I am? It starts with 14 "IARC"? 15 A. Yes. 16 Q. Says (as read): 17 "IARC has stated that a causal 18 association between exposure to 19 asbestos and cancer of the ovary 20 was clearly established based on 21 strongly positive cohort mortality 22 studies of women with occupational 23 exposure to asbestos, as well as 24 studies of women with 25 environmental exposure to</p>	<p>1 Dr. Moorman. 2 A. Yes. 3 Q. Actually, 256 is where it carries into. And 4 on page 256, there's a section entitled "syntheses." 5 Do you see where I am, Dr. Moorman? 6 A. Yes. 7 Q. Okay. And if you look at the right-hand 8 column, it's the first full paragraph in the middle of 9 the page. 10 A. Yes. 11 Q. And there, the IARC states that (as read): 12 "The working group noted that a 13 causal association between 14 exposure to asbestos and cancer of 15 the ovary was clearly established 16 based on five strongly positive 17 cohort mortality studies of women 18 with heavy occupational exposure 19 to asbestos." 20 Do you see that? 21 A. Yes. 22 Q. Okay. And so the IARC then goes on to say, 23 in the next sentence, that the conclusion (as read): 24 "Received additional support from 25 studies showing that women and</p>
Page 91	Page 93
<p>1 asbestos." 2 A. Yes. 3 Q. Do you see where I was reading? 4 A. Yes. 5 Q. To be clear, Dr. Moorman, that's not 6 precisely how IARC has stated that, is it? 7 MS. PARFITT: Objection. Form. 8 THE WITNESS: I -- 9 BY MR. JAMES: 10 Q. I'm sorry, Doctor. 11 If I may, Dr. Moorman, I'll just provide you 12 a copy. Is that okay? 13 A. Okay. 14 Q. I'm going to mark as Exhibit 14 a copy of 15 the -- what we're referring to as the asbestos 16 monograph that's 100C. 17 (Exhibit No. 14 was marked for identification.) 18 MS. PARFITT: Mr. James, just for the 19 record, that's not the entire 100C monograph, is it? 20 MR. JAMES: Thank you. Thank you. Let 21 me clarify. This is excerpts of -- Exhibit 14 is 22 excerpts of the monograph. 23 MS. PARFITT: Thank you. 24 BY MR. JAMES: 25 Q. Okay. And if we turn to page 254,</p>	<p>1 girls with environmental, but not 2 occupational exposure to asbestos, 3 had positive, but nonsignificant, 4 increases in both ovarian cancer 5 incidence and mortality." 6 Do you see that? 7 A. Yes. 8 Q. And so the IARC's conclusion here with 9 respect to asbestos and ovarian cancer. 10 Again, this conclusion is being made outside 11 the context of talcum powders; correct? 12 A. Right. This is based on asbestos exposure. 13 Q. And the way that IARC has structured this 14 paragraph is that they have said that they've based 15 their conclusion on the occupational studies; correct? 16 MS. PARFITT: Objection. Form. 17 THE WITNESS: Yes. 18 BY MR. JAMES: 19 Q. And then they do note the additional support 20 after that sentence; correct? 21 MS. PARFITT: Objection to form. 22 THE WITNESS: Yes. 23 BY MR. JAMES: 24 Q. Okay. And just to be clear, the IARC here 25 acknowledges that the non-occupational studies report</p>

24 (Pages 90 to 93)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 94	Page 96
<p>1 nonstatistically significant associations; correct?</p> <p>2 A. They note "positive, though nonsignificant</p> <p>3 increases."</p> <p>4 Yes, that's what it states.</p> <p>5 Q. And if you turn with me to page 280 of the</p> <p>6 same monograph, Dr. Moorman, with respect to talcum</p> <p>7 powder, specifically, on the right-hand column of</p> <p>8 page 280, it's the third full paragraph down, the IARC</p> <p>9 monograph states (as read):</p> <p>10 "The association between exposure</p> <p>11 to talc, potential or retrograde</p> <p>12 translocation to the ovarian</p> <p>13 epithelium, and the development of</p> <p>14 an ovarian cancer is</p> <p>15 controversial."</p> <p>16 Do you see where I was reading that?</p> <p>17 A. I do see that.</p> <p>18 Q. So in the same monograph where they're</p> <p>19 talking about asbestos and ovarian cancer in general,</p> <p>20 the IARC calls out the issue of talcum powder as a</p> <p>21 controversial association; correct?</p> <p>22 MS. PARFITT: Objection. Form.</p> <p>23 THE WITNESS: That's what it states,</p> <p>24 yes.</p> <p>25</p>	<p>1 A. Yes.</p> <p>2 Q. The IARC has not concluded that the presence</p> <p>3 of asbestos in talc powders renders such powders as</p> <p>4 carcinogenic, has it?</p> <p>5 MS. PARFITT: Objection. Form.</p> <p>6 THE WITNESS: I can't recall if they</p> <p>7 have made that conclusion or not.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. You understand that when the IARC separately</p> <p>10 assessed talcum powders in the other monograph that</p> <p>11 we're talking about, they classified perineal talc use</p> <p>12 as a 2B do you know that?</p> <p>13 MS. PARFITT: And you're referring to</p> <p>14 the 2010 monograph?</p> <p>15 MR. JAMES: Yes, and I think that's</p> <p>16 what I said, and if I didn't, my apologies.</p> <p>17 THE WITNESS: Yes, to be a possible</p> <p>18 carcinogenic.</p> <p>19 BY MR. JAMES:</p> <p>20 Q. Okay. And by designating perineal talc use</p> <p>21 as a 2B, the IARC is not concluding that it is, in</p> <p>22 fact, a carcinogenic; correct?</p> <p>23 A. What they are concluding is that it is a</p> <p>24 possible carcinogen.</p> <p>25 Q. IARC has multiple classifications; correct?</p>
Page 95	Page 97
<p>1 BY MR. JAMES:</p> <p>2 Q. Did you cite that conclusion in your report?</p> <p>3 MS. PARFITT: Objection. Form.</p> <p>4 THE WITNESS: I did not specifically</p> <p>5 cite this, because, you know, again, this was a</p> <p>6 conclusion made IARC 2010, and additional data has</p> <p>7 accumulated. And so I think that we're seeing that if</p> <p>8 they had -- you know, of course, I have no way of</p> <p>9 knowing what they would conclude, but I think that, in</p> <p>10 light of additional evidence that has arisen since the</p> <p>11 time that this report was written, a different</p> <p>12 conclusion could have been reached.</p> <p>13 MR. JAMES: Okay. And I object to the</p> <p>14 nonresponsive portion of that answer.</p> <p>15 BY MR. JAMES:</p> <p>16 Q. And for purposes of the record, Dr. Moorman,</p> <p>17 the monograph that we're looking at here together was</p> <p>18 published in 2012; correct?</p> <p>19 A. That is correct.</p> <p>20 Q. I think that you're probably thinking of the</p> <p>21 other monograph, which is the 2010 monograph; correct?</p> <p>22 When you said 2010?</p> <p>23 A. Well, I was looking at what was stated in</p> <p>24 that paragraph.</p> <p>25 Q. Fair enough. Fair enough.</p>	<p>1 A. That is correct.</p> <p>2 Q. If they characterize -- if they -- if they</p> <p>3 characterize something as a carcinogen, they label it</p> <p>4 as a Group 1; correct?</p> <p>5 A. That is correct.</p> <p>6 Q. If they characterize something as a probable</p> <p>7 carcinogen, they label it a 2A; correct?</p> <p>8 A. That is correct.</p> <p>9 Q. And if they characterize something as a</p> <p>10 possible, it's a 2B; correct?</p> <p>11 A. That is correct.</p> <p>12 Q. And the IARC has settled on 2B with talc --</p> <p>13 and with perineal talc use; correct?</p> <p>14 MS. PARFITT: Objection. Form.</p> <p>15 THE WITNESS: Once again, at the time</p> <p>16 of the report, that's what they decided on.</p> <p>17 BY MR. JAMES:</p> <p>18 Q. The opinions that you're offering in</p> <p>19 litigation in this MDL report are contrary to those</p> <p>20 reached by IARC; correct?</p> <p>21 MS. PARFITT: Objection. Form.</p> <p>22 THE WITNESS: No. I don't think that</p> <p>23 they are contrary. I think possible carcinogen --</p> <p>24 they are not saying it is not a carcinogen; they're</p> <p>25 saying a possible carcinogen.</p>

25 (Pages 94 to 97)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 98	Page 100
<p>1 And I -- my report, with the additional 2 information that has been published since the time 3 that this report was done, I think that it strengthens 4 the conclusions. And that's why I felt comfortable 5 saying that it is a cause of ovarian cancer. 6 BY MR. JAMES: 7 Q. And so what you're saying is different than 8 what the IARC said in 2010; correct? 9 MS. PARFITT: Objection. Misstates her 10 testimony. Asked and answered. 11 THE WITNESS: I'm saying that there is 12 additional evidence that has arisen, and it 13 strengthens the -- it strengthens the evidence for the 14 association between talc and ovarian cancer. 15 BY MR. JAMES: 16 Q. And in 2010, IARC did not determine that 17 perineal talc use was carcinogenic; correct? 18 A. They said -- 19 MS. PARFITT: Objection. Misstates 20 testimony. 21 THE WITNESS: -- it was a possible 22 carcinogen. 23 MR. JAMES: I didn't misstate any 24 testimony. I didn't state anything about her 25 testimony. I asked a question.</p>	<p>1 MR. MIZGALA: There's a big difference. 2 MR. JAMES: Let's just move on. 3 MS. PARFITT: I didn't say 4 "peritoneal." That may be what the court reporter -- 5 And, Sophie, the record should reflect that 6 when we are saying -- for the most part, when someone 7 wants to say something, it's "perineal" -- 8 MR. JAMES: May we continue? 9 MS. PARFITT: I appreciate it. Thank 10 you. 11 I just want to help the court reporter out, 12 Scott. I'm sure you want a very clear record. 13 And, James, thank you very much for making 14 sure it is clear. 15 So, Sophie, thank you. When we say 16 "perineal," we mean "perineal." Not your fault at 17 all. 18 Thank you. 19 MR. JAMES: Are we good? 20 MS. PARFITT: We are so good. 21 BY MR. JAMES: 22 Q. In 2010, the IARC declared talc -- perineal 23 talc a 2B; correct? 24 A. That is correct. 25 Q. Okay. In 2010, the evidence that was before</p>
Page 99	Page 101
<p>1 MS. PARFITT: You actually 2 misrepresented her answer in your question. That was 3 my objection. You can go ahead. 4 MR. JAMES: If you'd like to read the 5 realtime, I didn't say anything about what she 6 testified to. I asked a question -- 7 MS. PARFITT: You said, "In 2010" -- 8 (Over-speaking.) 9 MR. JAMES: But if you want to continue 10 to do that all day -- 11 MS. PARFITT: -- "IARC did not 12 determine that peritoneal [sic] talc was carcinogenic; 13 correct?" 14 Just before that, she had said that it was 15 carcinogenic. 16 MR. JAMES: But I wasn't misstating her 17 testimony. 18 MS. PARFITT: Well, when you say that, 19 and she answered the question before that that's not 20 what IARC said, and then you say that is what IARC 21 says, you are misstating her testimony. 22 MR. MIZGALA: It's "perineal," not 23 "peritoneal." 24 MR. JAMES: Let's just move on. If you 25 continue to --</p>	<p>1 the IARC -- was the evidence at that time sufficient 2 for IARC to have said something more than 2B? 3 MS. PARFITT: Objection. Form. 4 THE WITNESS: I'm not quite sure. 5 BY MR. JAMES: 6 Q. You want me to rephrase? 7 A. Yes, if you wouldn't mind. 8 Q. You alluded to evidence that has -- and if 9 I'm misstating your testimony, Ms. Parfitt, please 10 object, because now I actually am talking about your 11 testimony. 12 A. Okay. 13 Q. But you alluded earlier that evidence has 14 developed since the 2010 monograph; correct? 15 A. Right. 16 Q. And so my question is, in your expert 17 assessment in 2010, when the IARC declared perineal 18 talc use to be a 2B, was the evidence at that snapshot 19 in time sufficient to support something more than 2B, 20 less than 2B, or did the IARC get it right? 21 MS. PARFITT: Objection. Form. 22 THE WITNESS: I -- I think that their 23 statement that it is a possible carcinogen -- I don't 24 know if you can -- you know, possible versus probable, 25 it's -- I don't know that there is any checklist to</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 102	Page 104
<p>1 say this level of evidence would lead it to possible</p> <p>2 versus probable.</p> <p>3 And so to say whether or not they got it</p> <p>4 right, I don't know how to answer that question.</p> <p>5 I think that they certainly are indicating that there</p> <p>6 was evidence indicating a problem, and now we have</p> <p>7 more evidence that strengthens the -- I think there's</p> <p>8 greater evidence that talc can cause ovarian cancer.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. If someone had asked you to assess the body</p> <p>11 of scientific and medical literature in 2010 on the</p> <p>12 claim that talcum powder products cause ovarian</p> <p>13 cancer, would you have opined in 2010 that the</p> <p>14 evidence was sufficient to state that talcum powder</p> <p>15 products generally cause ovarian cancer?</p> <p>16 MS. PARFITT: Objection. Form.</p> <p>17 THE WITNESS: I think that it is</p> <p>18 impossible to say with certainty what -- at that point</p> <p>19 in time what would I have opined? I think that, as we</p> <p>20 are well aware, the body of literature has continued</p> <p>21 to grow over time. I think that it has only</p> <p>22 strengthened over time. At what point would I have</p> <p>23 been able to opine that talc is a cause of ovarian</p> <p>24 cancer? I can't pinpoint that exactly.</p> <p>25</p>	<p>1 MS. PARFITT: Objection to form.</p> <p>2 THE WITNESS: I -- when I look at some</p> <p>3 of the studies, there are limitations, as there are</p> <p>4 with -- I would say, with any study of humans and</p> <p>5 cancer.</p> <p>6 One of the things that comes to mind as a</p> <p>7 possible limitation is that, in the occupational</p> <p>8 studies, the cohorts are relatively small for looking</p> <p>9 at cancer outcomes. So in many -- maybe the</p> <p>10 majority -- of them, they had a few hundred people in</p> <p>11 the cohort; and, when you looked at the expected</p> <p>12 versus the observed number of cases, we're talking</p> <p>13 about a handful of cases.</p> <p>14 So it might be, you know, two or three</p> <p>15 observed cases versus .6 expected or something like</p> <p>16 that.</p> <p>17 So that is a limitation of all of -- as</p> <p>18 I recall, all of the occupational cohort studies that</p> <p>19 the sample cites of the cohort.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. Would you also acknowledge that another</p> <p>22 limitation to that body of literature is the fact that</p> <p>23 it's in the occupational context?</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25 THE WITNESS: I don't necessarily</p>
Page 103	Page 105
<p>1 BY MR. JAMES:</p> <p>2 Q. And when you say in 2010 IARC declared talc a</p> <p>3 2B, I think the phrasing that you used was that they</p> <p>4 were saying that there was, quote, a problem.</p> <p>5 Is that what you said?</p> <p>6 A. I think that I said something to that effect.</p> <p>7 Q. Okay. You understand that the IARC's</p> <p>8 classification system does have a checklist of sorts</p> <p>9 to determine if something is a 1, a 2A, or a 2B;</p> <p>10 correct? Or a 3 and so on and so forth.</p> <p>11 A. I am not familiar with the exact checklist.</p> <p>12 Yes.</p> <p>13 Q. Do you understand that, if IARC declares</p> <p>14 something a 2B, it's concluding that chance, bias, and</p> <p>15 confounding cannot be ruled out? Did you know that?</p> <p>16 A. Again, off the top of my head, I cannot</p> <p>17 recall exactly what are their -- you know, as you put</p> <p>18 it, what is their checklist.</p> <p>19 Q. Returning now back to the body of literature</p> <p>20 on asbestos and ovarian cancer, you have testified</p> <p>21 that you have reviewed that body of literature;</p> <p>22 correct?</p> <p>23 A. Yes.</p> <p>24 Q. Do you recognize any limitations to that body</p> <p>25 of literature?</p>	<p>1 consider that a limitation. That is where people had</p> <p>2 exposure to this -- to asbestos in an occupational</p> <p>3 setting. So if you want to look at the health effects</p> <p>4 of that exposure, that's exactly where you would do</p> <p>5 the study.</p> <p>6 BY MR. JAMES:</p> <p>7 Q. Do you agree that the body of literature in</p> <p>8 the occupational context, which looks at exposure to</p> <p>9 asbestos in the occupational setting, is different</p> <p>10 than the allegation that exposure to contaminated</p> <p>11 talcum powder products causes ovarian cancer?</p> <p>12 A. The -- I agree that there is some difference</p> <p>13 in the exposure, but it's part of the body of</p> <p>14 literature. It's -- people exposed in this way, they</p> <p>15 are at increased risk for ovarian cancer. So they may</p> <p>16 have different levels of exposure, different routes of</p> <p>17 exposure, but it's all part of the body of literature.</p> <p>18 Q. You would agree that someone that's exposed</p> <p>19 to asbestos-containing products in a factory</p> <p>20 environment for a full workday is experiencing a</p> <p>21 different level of exposure to someone who is using</p> <p>22 allegedly contaminated asbestos talcum powder</p> <p>23 products?</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25</p>

27 (Pages 102 to 105)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 106</p> <p>1 BY MR. JAMES: 2 Q. Let me rephrase that, because I jumbled that 3 up. 4 Would you agree that the level of exposure 5 that someone would experience in the occupational 6 setting to asbestos products is qualitatively 7 different than what Plaintiffs are alleging in this 8 case, which is exposure to talcum powder products that 9 are allegedly contaminated with asbestos? 10 A. I acknowledge that the exposures are 11 different. It's how they are applied -- or, you know, 12 the -- you know, we're talking about exposure to the 13 genital area when we're talking about talcum powder 14 products that may contain asbestos, where we would not 15 expect to have genital exposure of asbestos in an 16 occupational setting. 17 So, yes, there are differences. 18 Q. Do you acknowledge another limitation in the 19 body of literature that IARC looked at to be 20 misclassification? 21 A. In epidemiology, we -- we recognize that 22 there is likely to be misclassification in any 23 epidemiologic study that you do. This is not a 24 situation like with laboratory studies of animals 25 where you can control every exposure, measure it very</p>	<p style="text-align: right;">Page 108</p> <p>1 meta-analysis before; correct? 2 A. I have. 3 Q. You don't have any discussion of the Reid 4 paper in your report; correct? 5 A. I don't -- I don't believe I do. 6 Q. Do you understand that the Reid paper 7 conflicts in part with the claim that asbestos is a 8 cause of ovarian cancer? 9 MS. PARFITT: Objection. 10 THE WITNESS: I know what they -- what 11 these authors concluded. 12 BY MR. JAMES: 13 Q. And if you look with me on page 1294, 14 Dr. Moorman, in the "conclusions" section, you see at 15 the bottom of that paragraph, with the sentence 16 beginning with the word "however" -- it's sort of 17 three-fourths of the way down -- the authors state 18 (as read): 19 "However, the authors of this 20 article suggest that the IARC 21 decision to determine asbestos 22 exposure as a cause of ovarian 23 cancer was premature and not 24 wholly supported by the evidence." 25 Do you see where I read that?</p>
<p style="text-align: right;">Page 107</p> <p>1 accurately. 2 So some potential misclassification is 3 possible, as it is in any epidemiologic study. 4 Q. And the issue of misclassification has been 5 specifically acknowledged in this body of literature; 6 correct? 7 MS. PARFITT: Objection to form. 8 THE WITNESS: Can you be more specific 9 about which misclassification you're referring to? 10 BY MR. JAMES: 11 Q. Sure. So what I'm referring to is 12 misclassification of disease. 13 Do you -- do you recall that, in this body 14 of literature, there is discussion that, given the 15 small number of cases which you described earlier, 16 misclassification -- the potential for disease 17 misclassification is a limitation to this body of 18 literature? 19 A. I am aware that that is an issue that has 20 been discussed in this literature, yes. 21 MR. JAMES: And I'm going to mark as 22 Exhibit No. 15 the Reid paper. 23 (Exhibit No. 15 was marked for identification.) 24 BY MR. JAMES: 25 Q. And, Dr. Moorman, you've seen this Reid</p>	<p style="text-align: right;">Page 109</p> <p>1 A. I do see that. 2 Q. Okay. And so you acknowledge here that the 3 authors of this paper have called into question the 4 IARC decision; correct? 5 MS. PARFITT: Objection. Form. 6 THE WITNESS: I see what they have 7 stated here, that -- 8 BY MR. JAMES: 9 Q. And -- 10 A. -- that is their opinion, yes. 11 Q. Excuse me, Doctor. My apologies. 12 A. Yes. 13 Q. And, again, this paper is assessing the 14 IARC's conclusion about asbestos and ovarian cancer in 15 general; correct? 16 MS. PARFITT: Objection. Form. 17 BY MR. JAMES: 18 Q. It's not -- this article isn't pertaining to 19 the issue of alleged asbestos contamination in talcum 20 powder products, is it? 21 A. Right. This is focused just on asbestos and 22 ovarian cancer. 23 Q. And if you look at the bottom of that -- the 24 very last sentence in that paragraph, you see where 25 the authors there discuss the potential problem of</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 110	Page 112
<p>1 misclassification?</p> <p>2 A. I'm sorry, where are you?</p> <p>3 Q. It's the very last sentence, Doctor.</p> <p>4 A. Yes, I see what is written there.</p> <p>5 Q. So this article conflicts with your</p> <p>6 litigation opinion; correct?</p> <p>7 MS. PARFITT: Objection. Form.</p> <p>8 THE WITNESS: This reflects the opinion</p> <p>9 of these authors. There was another meta-analysis of</p> <p>10 asbestos and ovarian cancer that I believe was</p> <p>11 published in the same year. And as I recall, the</p> <p>12 conclusions of those authors, while acknowledging</p> <p>13 potential misclassification of disease, they felt like</p> <p>14 the evidence was adequate to rule that out as a</p> <p>15 possible source of bias that would explain the</p> <p>16 association that was observed.</p> <p>17 BY MR. JAMES:</p> <p>18 Q. And you're speaking of the Camargo article,</p> <p>19 I believe?</p> <p>20 A. Yes.</p> <p>21 Q. And have you separately assessed the issue of</p> <p>22 misclassification and whether, in your mind, that</p> <p>23 presents a significant enough problem to call into</p> <p>24 question the IARC conclusions?</p> <p>25 MS. PARFITT: Objection. Form.</p>	<p>1 Q. Did you review those articles?</p> <p>2 A. I did look at them, and as I recall, almost</p> <p>3 all of those -- the miners and -- almost all of the</p> <p>4 miners, and probably the millers, they were focusing</p> <p>5 primarily on males who were the people who were mostly</p> <p>6 involved in that type of work.</p> <p>7 Q. You would agree with me that if talcum</p> <p>8 powder, that is used in cosmetic talc products, is, in</p> <p>9 fact, contaminated with asbestos, then you would</p> <p>10 expect to see increased cancer incidence rates, for</p> <p>11 example, of mesothelioma, in cosmetic talc miners and</p> <p>12 millers; correct?</p> <p>13 MS. PARFITT: Objection. Form.</p> <p>14 THE WITNESS: I wouldn't be surprised</p> <p>15 to see that, yes.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. And did you know that that body of literature</p> <p>18 reports no increased cancer incidence in talc miners</p> <p>19 and millers?</p> <p>20 A. It has been a while since I have looked at</p> <p>21 those papers, so I don't remember exactly what they</p> <p>22 reported.</p> <p>23 Q. And those papers are not discussed in your</p> <p>24 report; correct?</p> <p>25 A. Once again, I was focusing primarily on</p>
Page 111	Page 113
<p>1 THE WITNESS: Let me read your...</p> <p>2 I believe that I was convinced by the</p> <p>3 information presented in the Camargo article that</p> <p>4 I don't think that misclassification was enough of a</p> <p>5 problem to change the conclusion.</p> <p>6 BY MR. JAMES:</p> <p>7 Q. Are you familiar with -- did you undertake a</p> <p>8 Bradford Hill analysis of the literature on asbestos</p> <p>9 and ovarian cancer to reach the conclusion that</p> <p>10 asbestos is a cause of ovarian cancer?</p> <p>11 A. I didn't -- did not do the Bradford Hill</p> <p>12 analysis as I did with the talcum powder products and</p> <p>13 ovarian cancer. I felt like it was pretty well</p> <p>14 accepted.</p> <p>15 Q. Did you consider a body of literature</p> <p>16 commonly referred to as the "miners and millers</p> <p>17 studies"?</p> <p>18 A. Please -- I'm sorry. When you talk about the</p> <p>19 miners and millers studies, I'm not sure that I'm on</p> <p>20 the same page with you.</p> <p>21 Q. Are you familiar -- are you aware of the fact</p> <p>22 that there's a body of literature that has looked at</p> <p>23 cancer incidence rates in miners and millers of talc?</p> <p>24 A. Yes, I am aware of some of those articles.</p> <p>25 Yes.</p>	<p>1 ovarian cancer. And as many of these were on male</p> <p>2 subjects, I had looked at them, but they were of</p> <p>3 somewhat lesser importance to my review.</p> <p>4 Q. If --</p> <p>5 MS. PARFITT: I don't want to</p> <p>6 interrupt, and maybe a few follow-up questions. We're</p> <p>7 probably into about an hour and 20 minutes or so. But</p> <p>8 I don't want to interrupt your flow either.</p> <p>9 MR. JAMES: I can finish up in a few,</p> <p>10 or if you need a break now, we can take it now.</p> <p>11 THE WITNESS: Let's finish up in a few.</p> <p>12 MR. JAMES: And when I say "finish up,"</p> <p>13 I just mean this line. I apologize for that. That</p> <p>14 was misleading, I think.</p> <p>15 Sure. Give me a couple more, and then we'll</p> <p>16 take a break.</p> <p>17 THE WITNESS: Yeah, we can go a few</p> <p>18 more minutes.</p> <p>19 MS. PARFITT: Thank you, Scott.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. If asbestos-contaminated talcum powder</p> <p>22 products have existed on the market for some period of</p> <p>23 time, wouldn't you expect to find higher incidence</p> <p>24 rates of other cancers of talcum powder users?</p> <p>25 MS. PARFITT: Objection. Form.</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 114</p> <p>1 THE WITNESS: It depends.</p> <p>2 BY MR. JAMES:</p> <p>3 Q. For example -- oh, I'm sorry. I thought you</p> <p>4 were done.</p> <p>5 A. I am done. Go ahead.</p> <p>6 Q. For example, if asbestos has contaminated</p> <p>7 talcum powder products for some period of time,</p> <p>8 wouldn't you expect to see higher rates of</p> <p>9 mesothelioma in users of cosmetic talcum powder</p> <p>10 products?</p> <p>11 A. You know, mesothelioma is an exceedingly rare</p> <p>12 cancer, and I don't know -- I don't know to what</p> <p>13 extent it has been -- talcum powder products --</p> <p>14 cosmetic talcum powder products has been examined as a</p> <p>15 risk factor for that.</p> <p>16 Q. Are you aware of any data showing that users</p> <p>17 of cosmetic talcum powder products are at greater risk</p> <p>18 of mesothelioma, asbestosis, or any other</p> <p>19 asbestos-related diseases?</p> <p>20 MS. PARFITT: Objection. Form.</p> <p>21 THE WITNESS: I can't think of that</p> <p>22 data right offhand, no.</p> <p>23 MR. JAMES: Okay. And how about now</p> <p>24 for a break?</p> <p>25 THE WITNESS: Okay.</p>	<p style="text-align: right;">Page 116</p> <p>1 MS. PARFITT: Objection. Form.</p> <p>2 THE WITNESS: I considered it as part</p> <p>3 of the constituents of the talcum powder products. My</p> <p>4 overall opinion is based on exposure to talcum powder</p> <p>5 products and whatever constituents are in there,</p> <p>6 including the fibrous talc.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. Given that you have opined in your MDL report</p> <p>9 for the first time on fibrous talc and did not provide</p> <p>10 that opinion in the Ingham case, can you tell me what</p> <p>11 you're basing your opinion on with regard to the</p> <p>12 fibrous talc?</p> <p>13 MS. PARFITT: Objection.</p> <p>14 Hey, Scott, if I can ask -- I'm sorry, it</p> <p>15 isn't rolling. Is there some reason? I don't want to</p> <p>16 interrupt. We'll deal with it.</p> <p>17 THE COURT REPORTER: I can come over</p> <p>18 and do it, but we'll have to go off.</p> <p>19 MS. PARFITT: Sorry about that.</p> <p>20 THE VIDEOGRAPHER: Going off the record</p> <p>21 at 12:40 p.m.</p> <p>22 (Off the record.)</p> <p>23 THE VIDEOGRAPHER: Back on record at</p> <p>24 12:41 p.m.</p> <p>25</p>
<p style="text-align: right;">Page 115</p> <p>1 MS. PARFITT: Thank you.</p> <p>2 THE VIDEOGRAPHER: Going off record at</p> <p>3 11:45 a.m.</p> <p>4 (Recess taken from 11:45 a.m. to 12:39 p.m.)</p> <p>5 THE VIDEOGRAPHER: Back on record at</p> <p>6 12:39 p.m.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. Dr. Moorman, you include in your MDL report</p> <p>9 references to "talc occurring in the fibrous habit."</p> <p>10 Do you recall referring to that in your</p> <p>11 report?</p> <p>12 A. Yes, I do.</p> <p>13 Q. That terminology is new to the MDL for you,</p> <p>14 isn't it?</p> <p>15 MS. PARFITT: Objection. Form.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. I'll clarify.</p> <p>18 A. Please. Please do.</p> <p>19 Q. You did not -- in your Ingham testimony,</p> <p>20 where you provided your opinions in the Ingham case,</p> <p>21 you did not refer to "fibrous talc," did you?</p> <p>22 A. No, I don't believe I did.</p> <p>23 Q. So that -- sorry.</p> <p>24 So that's a new component of your opinion in</p> <p>25 the MDL?</p>	<p style="text-align: right;">Page 117</p> <p>1 BY MR. JAMES:</p> <p>2 Q. Dr. Moorman, before the quick break -- I'll</p> <p>3 just restate the question.</p> <p>4 A. Okay.</p> <p>5 Q. So what do you base your opinions on with</p> <p>6 regard to fibrous talc?</p> <p>7 A. Okay. My opinion, I guess, is -- again, it's</p> <p>8 always been based on the constituents of the talcum</p> <p>9 powder products. And so maybe clarifying based on</p> <p>10 maybe further reading on the constituents of, like,</p> <p>11 asbestiform talc, that this again contributes to the</p> <p>12 biological plausibility of it, that this is another</p> <p>13 potential constituent of the talcum powder product</p> <p>14 that could contribute to ovarian cancer risk.</p> <p>15 Q. So one component of your opinion is that</p> <p>16 there is fibrous talc in talcum powder products;</p> <p>17 correct?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. And given that that is a new opinion,</p> <p>20 I am attempting to source the bases for that opinion.</p> <p>21 Are the opinions that you have about the</p> <p>22 presence of fibrous talc in talcum powder products</p> <p>23 based upon the same materials that you rely on for</p> <p>24 your opinions about the presence of asbestos in talcum</p> <p>25 powder products?</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 118	Page 120
<p>1 MS. PARFITT: Objection. Form. As far</p> <p>2 as a new opinion.</p> <p>3 THE WITNESS: I'm sorry, let me read</p> <p>4 that.</p> <p>5 So my opinions about the presence of fibrous</p> <p>6 talc in talcum powder products is based on some of the</p> <p>7 same materials that have done analyses of talcum</p> <p>8 powder products, yeah.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. Would that include the Longo -- Dr. Longo</p> <p>11 litigation testing?</p> <p>12 A. I believe that he did make some mention of</p> <p>13 that in his report, yes.</p> <p>14 Q. And other -- would that include other</p> <p>15 litigation reports that you reviewed?</p> <p>16 MS. PARFITT: Objection. Form.</p> <p>17 THE WITNESS: I'm -- precisely where</p> <p>18 the information came from, that there is fibrous talc</p> <p>19 in talcum powder products, I -- I don't recall exactly</p> <p>20 where -- where I gleaned that information.</p> <p>21 BY MR. JAMES:</p> <p>22 Q. And did you -- did you ask counsel if there</p> <p>23 was any information provided by Johnson & Johnson in</p> <p>24 the talc litigation rebutting the claim that there's</p> <p>25 fibrous talc present in the products?</p>	<p>1 BY MR. JAMES:</p> <p>2 Q. Would you defer to others with regard to the</p> <p>3 question of whether heavy metals are in the talcum</p> <p>4 powder products?</p> <p>5 A. I -- by deferring to others, okay, I clearly</p> <p>6 do not do the analyses of those -- of those -- those</p> <p>7 types of analyses myself, so I am relying on a report.</p> <p>8 In this case, it was a report done by Dr. Crowley.</p> <p>9 Q. Just to clarify, and Ms. Parfitt can correct</p> <p>10 me if I'm wrong, but when you refer to Dr. Crowley's</p> <p>11 report, are you referring to Dr. Crowley's report</p> <p>12 about fragrances?</p> <p>13 A. And I believe that it was not just</p> <p>14 fragrances, but it was a number of substances that he</p> <p>15 analyzed in that -- that he addressed in his analysis.</p> <p>16 Q. Did you do any independent searching for</p> <p>17 materials or scientific literature on the allegation</p> <p>18 that heavy metals in cosmetic talc powders cause</p> <p>19 ovarian cancer?</p> <p>20 MS. PARFITT: Objection.</p> <p>21 THE WITNESS: Okay. I'm reading your</p> <p>22 question again.</p> <p>23 No. I -- the -- what I looked at in regards</p> <p>24 to heavy metals -- again, we have this report</p> <p>25 indicating that these can be found in some talcum</p>
Page 119	Page 121
<p>1 MS. PARFITT: Objection. Form.</p> <p>2 THE WITNESS: No, I did not</p> <p>3 specifically ask them for that information.</p> <p>4 BY MR. JAMES:</p> <p>5 Q. Have you relied on any epidemiology</p> <p>6 substantiating a claim that fibrous talc is</p> <p>7 carcinogenic?</p> <p>8 A. I am not aware of any epidemiologic</p> <p>9 literature that specifically addressed that question.</p> <p>10 Q. Turning to your opinions on heavy metals,</p> <p>11 Dr. Moorman, you have opined in your report about</p> <p>12 chromium, nickel, and cobalt; correct?</p> <p>13 A. Yes, I have.</p> <p>14 Q. Yet your opinions in the MDL report about the</p> <p>15 alleged presence of chromium, nickel, and cobalt in</p> <p>16 talcum powder products is new in the sense that you</p> <p>17 did not express that opinion in the Ingham case;</p> <p>18 correct?</p> <p>19 MS. PARFITT: Objection. Misstates her</p> <p>20 testimony -- our testimony.</p> <p>21 THE WITNESS: I think the gist of my</p> <p>22 opinions are based on talcum powder products and</p> <p>23 whatever constituents are in there; so talc, asbestos,</p> <p>24 any fragrances or other contaminants that may be in</p> <p>25 there. So it's based on the product.</p>	<p>1 powder products, and then again we have data</p> <p>2 indicating that these heavy metals can cause certain</p> <p>3 types of cancer.</p> <p>4 So it contributes to the biological</p> <p>5 plausibility that there are substances in the talcum</p> <p>6 powder products that could lead to cancer.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. With regard to opinions about the presence of</p> <p>9 heavy metals in talcum powder products, did you ask to</p> <p>10 see any information or materials presented in the talc</p> <p>11 litigation by Johnson & Johnson as to that claim?</p> <p>12 A. No, I did not.</p> <p>13 Q. Did you do any separate analysis of the</p> <p>14 talcum powder products to determine the presence of</p> <p>15 heavy metals in these products?</p> <p>16 A. I did not do any analyses of talcum powder</p> <p>17 products.</p> <p>18 Q. Do you have any knowledge concerning the</p> <p>19 testing that is performed by Johnson & Johnson and</p> <p>20 third parties with respect to constituent elements in</p> <p>21 the products?</p> <p>22 A. No. This is outside my area of expertise.</p> <p>23 Q. Do you have any information about allowable</p> <p>24 levels of constituent elements in the talcum powder</p> <p>25 products?</p>

31 (Pages 118 to 121)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 122	Page 124
<p>1 A. No, I do not.</p> <p>2 Q. Do you have any basis to believe that if</p> <p>3 talcum powder products exceeded allowable levels for</p> <p>4 constituent elements, that those products went to</p> <p>5 market?</p> <p>6 MS. PARFITT: Objection. Form.</p> <p>7 THE WITNESS: No, I -- I don't have any</p> <p>8 information in that regard.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. Okay. Turning to -- with -- to your opinion</p> <p>11 on -- strike that.</p> <p>12 Do you hold the independent opinion that</p> <p>13 cadmium, chromium, and cobalt cause ovarian cancer?</p> <p>14 MS. PARFITT: Objection. Form.</p> <p>15 THE WITNESS: I do -- I am not aware of</p> <p>16 papers that have directly addressed those metals in</p> <p>17 relation to ovarian cancer risk. I am basing it more</p> <p>18 on the conclusions from IARC that they do have</p> <p>19 carcinogenic potential.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. And is the same true for nickel?</p> <p>22 A. Yes.</p> <p>23 Q. With regard to the alleged carcinogenicity of</p> <p>24 the constituent metal elements that you've identified</p> <p>25 in your report, did you consider anything other than</p>	<p>1 THE WITNESS: I -- I think that we do</p> <p>2 not have the data to specifically address that</p> <p>3 question specifically in regard to ovarian cancer.</p> <p>4 BY MR. JAMES:</p> <p>5 Q. With regard to the opinions you've expressed</p> <p>6 as to fragrances, is the sole basis of those opinions</p> <p>7 the value of work?</p> <p>8 A. That's the only document that I referred to.</p> <p>9 Q. And you understand --</p> <p>10 MR. JAMES: Ms. Parfitt, is it</p> <p>11 Dr. Crowley?</p> <p>12 MS. PARFITT: Dr. Crowley.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. Okay. Do you understand that Dr. Crowley is</p> <p>15 a paid expert in this litigation for the Plaintiffs?</p> <p>16 A. I do understand that.</p> <p>17 Q. Do you know if Dr. Crowley conducted any sort</p> <p>18 of risk assessment with regard to his calculations?</p> <p>19 A. I do not know that.</p> <p>20 Q. If Johnson & Johnson talcum powder products</p> <p>21 were not contaminated with asbestos, if you would</p> <p>22 accept that proposition from me, would you still hold</p> <p>23 the opinion that talcum powder products are a general</p> <p>24 cause of ovarian cancer?</p> <p>25 MS. PARFITT: Objection. Form.</p>
Page 123	Page 125
<p>1 the IARC monograph that you cited?</p> <p>2 A. No, I did not.</p> <p>3 Q. Did the IARC monograph that you cited include</p> <p>4 any assertion that the presence of these metals in</p> <p>5 talcum powders rendered those powders carcinogenic?</p> <p>6 A. I do not believe so.</p> <p>7 Q. Did the IARC 2010 monograph on talc include</p> <p>8 any assertion that the presence of heavy metals in</p> <p>9 those powders supports the 2B conclusion?</p> <p>10 MS. PARFITT: Objection. Form.</p> <p>11 THE WITNESS: I don't recall any</p> <p>12 mention of heavy metals in that monograph.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. Returning back to fragrances, in your MDL</p> <p>15 report, you refer to a report by Crowley. Did I say</p> <p>16 that right?</p> <p>17 A. I've never met the man, so I don't know how</p> <p>18 it's pronounced, but yes, that's what I said.</p> <p>19 Q. And that's the report you identified for the</p> <p>20 basis of your fragrance opinions; correct?</p> <p>21 A. Yes.</p> <p>22 Q. Do you have -- do you hold the independent</p> <p>23 opinion that the fragrance ingredients in talcum</p> <p>24 powder products renders those products carcinogenic?</p> <p>25 MS. PARFITT: Objection.</p>	<p>1 You can answer.</p> <p>2 THE WITNESS: Okay. The opinion</p> <p>3 I formed is based primarily on the epidemiologic data;</p> <p>4 and the epidemiologic data is based on talcum powder</p> <p>5 products, whatever is contained in them. And in study</p> <p>6 after study, we see increased risk for ovarian cancer.</p> <p>7 So whatever is contained in the talcum powder products</p> <p>8 leads me to conclude that it can cause ovarian cancer.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. And just to make sure that I understand your</p> <p>11 answer --</p> <p>12 A. Yes.</p> <p>13 Q. -- if the talcum powder products were not</p> <p>14 contaminated with asbestos, would you still reach the</p> <p>15 general cause opinion that you've offered in this</p> <p>16 case?</p> <p>17 MS. PARFITT: Objection. Form.</p> <p>18 THE WITNESS: I am -- I think that I've</p> <p>19 answered the question that it's based on talcum powder</p> <p>20 products, whatever is contained them -- in them. If</p> <p>21 it is shown that there is no asbestos, that doesn't</p> <p>22 change the fact that these dozens of epidemiologic</p> <p>23 studies have led to the conclusion of increased risk.</p> <p>24 BY MR. JAMES:</p> <p>25 Q. And does that same answer hold true if</p>

32 (Pages 122 to 125)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 126	Page 128
<p>1 I asked you the same question with respect to heavy 2 metals, fibrous talc, and fragrance ingredients? 3 MS. PARFITT: Objection. Form. 4 THE WITNESS: Yes. I am basing my 5 opinion on the use of talcum powder products and 6 whatever are -- whatever their constituents are. 7 BY MR. JAMES: 8 Q. As a professional epidemiologist -- is that a 9 fair way to say it? 10 A. Yes. 11 Q. Okay. As a professional epidemiologist, part 12 of your day-in, day-out work is to look at literature 13 on purported associations and make conclusions about 14 the strengths or weaknesses of that literature; 15 correct? 16 A. Yes. 17 Q. And you have done that before you were 18 brought into the talc litigation on a variety of 19 different exposures or other things evaluated for 20 associations; correct? 21 A. That is correct. 22 Q. And setting aside the issue of talcum powder 23 products, have you ever before, in assessing other 24 exposures or other associations, relied upon company 25 documents to reach your conclusions?</p>	<p>1 BY MR. JAMES: 2 Q. On page 4 of your -- actually, it's page 5 of 3 your report, Dr. Moorman. You refer on the top of 4 that page, in the first full paragraph, to the 5 Schildkraut 2016 study; correct? 6 A. First paragraph? Yes, that is correct. 7 Q. And you say in that paragraph -- and if 8 you're looking at the same paragraph as I am -- you 9 say there that (as read): 10 "This was the first study of talc 11 use and ovarian cancer focused 12 exclusively on African-American 13 women." 14 Correct? 15 A. Yes, I do. 16 Q. And to be clear, Dr. Moorman, that study did 17 not look exclusively at talc use, did it? 18 A. No. The purpose of the African American 19 cancer epidemiology study was to look at the 20 epidemiology of ovarian cancer in African American 21 broadly. So we've looked at a number of exposures. 22 Q. And specific to the issue of powder, the 23 Schildkraut 2016 study -- and I guess is the 24 underlying study, the AACES -- looks at body powder, 25 not talc per se; correct?</p>
Page 127	Page 129
<p>1 A. I -- I'm trying to think. 2 We have -- my colleagues and I have 3 published systematic reviews of oral contraceptive use 4 and ovarian cancer and other cancer risk. And as part 5 of that procedure -- this was through the Agency on 6 Healthcare Research and Quality, or AHRQ -- and as 7 part of that procedure trying to ensure that we have 8 all relevant documents, I believe that there was an 9 effort to see if there were any company document 10 studies that would be relevant to that systematic 11 review. 12 Q. What about any internal company testing 13 documents? Have you ever looked at any internal 14 company testing documents in assessing any association 15 that you've considered throughout your career? 16 A. No -- 17 MS. PARFITT: Objection. 18 THE WITNESS: -- I did not. 19 BY MR. JAMES: 20 Q. Have you ever considered any paid litigation 21 expert reports in assessing any other association that 22 you've looked at through your career? 23 MS. PARFITT: Objection. Form. 24 THE WITNESS: I -- I can't think of 25 another instance where I have done that.</p>	<p>1 A. That was how the question was asked in the 2 questionnaire, yes. 3 Q. Okay. And so the statements in your report 4 that state that the study looked at talc powder should 5 be clarified; correct? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: I think to be absolutely 8 precise, we should have -- I should have said body 9 powder. But based on other literature, most body 10 powder use is talcum powder product use. So I agree, 11 I could have been more precise in my language there. 12 BY MR. JAMES: 13 Q. And you understand body powders are made up 14 of a variety of constituents; correct? 15 A. Yes. 16 Q. There are baby powders that are made of 17 things other than talc; correct? 18 A. I believe so, that there are cornstarch 19 powders as well. 20 Q. And there are deodorizing powders that are 21 made of things other than talc; correct? 22 A. I believe so, yes. 23 Q. And you know cornstarch, if there's a baby 24 powder made of cornstarch, that product does not 25 contain talc; correct?</p>

33 (Pages 126 to 129)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 130	Page 132
<p>1 A. Yes.</p> <p>2 Q. Or -- I should clarify.</p> <p>3 If the version of the baby powder one is</p> <p>4 purchasing is labeled as a cornstarch product, it's</p> <p>5 cornstarch, not talc; correct?</p> <p>6 A. That is correct.</p> <p>7 Q. So the study participants in this study are</p> <p>8 not limited to talc users; correct?</p> <p>9 A. That is correct.</p> <p>10 Q. You also say in the report, in conjunction</p> <p>11 with these statements, that the study found a high</p> <p>12 prevalence of talc use; correct?</p> <p>13 A. Yes.</p> <p>14 Q. And we're looking at the same paragraph,</p> <p>15 Dr. Moorman. And, again, to be clear, the study</p> <p>16 didn't find that. The study, instead, found a high</p> <p>17 prevalence of powder use; correct?</p> <p>18 MS. PARFITT: Objection.</p> <p>19 THE WITNESS: Again, once I -- as I</p> <p>20 acknowledged earlier, I could have been more precise</p> <p>21 in the language, that it's -- I think that it -- based</p> <p>22 on our knowledge of the sales and other studies that</p> <p>23 have specifically reported on the types of powder use,</p> <p>24 the majority of the powder use would have been talc.</p> <p>25</p>	<p>1 anywhere else in your report, that for any genital use</p> <p>2 of body powder with an interview date before 2014, the</p> <p>3 results were not statistically significant; correct?</p> <p>4 MS. PARFITT: Objection.</p> <p>5 THE WITNESS: If you would give me just</p> <p>6 a moment to look through the report, I'd like to</p> <p>7 verify how I addressed that.</p> <p>8 I -- on page 23, I acknowledged that there</p> <p>9 was an attenuation of the odds ratio when comparing</p> <p>10 the women who were interviewed in the later time frame</p> <p>11 than in the earlier time frame.</p> <p>12 BY MR. JAMES:</p> <p>13 Q. Okay. And I'm looking at where you're</p> <p>14 looking, I believe, and it's the middle paragraph on</p> <p>15 page 23; correct?</p> <p>16 A. That is correct.</p> <p>17 Q. And there you say (as read):</p> <p>18 "The fact that the association was</p> <p>19 attenuated but not eliminated when</p> <p>20 considering the full study</p> <p>21 population suggested that the</p> <p>22 association was not due entirely</p> <p>23 to recall bias."</p> <p>24 Did I read that correctly?</p> <p>25 A. That is correct.</p>
Page 131	Page 133
<p>1 BY MR. JAMES:</p> <p>2 Q. You're not offering opinions on the MDL</p> <p>3 litigation about cornstarch, are you?</p> <p>4 A. No, I am not.</p> <p>5 Q. And you understand that the body of</p> <p>6 epidemiological literature that has developed over the</p> <p>7 last several decades has included findings looking at</p> <p>8 talc powders versus cornstarch powders versus non-talc</p> <p>9 powders; correct?</p> <p>10 A. Some studies, yes, have looked at the</p> <p>11 different powders.</p> <p>12 Q. And your -- the Schildkraut 2016 study didn't</p> <p>13 undertake the effort to make that distinction, did it?</p> <p>14 MS. PARFITT: Objection.</p> <p>15 THE WITNESS: I've already acknowledged</p> <p>16 that the question in the questionnaire just asked</p> <p>17 about body powder use.</p> <p>18 BY MR. JAMES:</p> <p>19 Q. You state that this study found a</p> <p>20 statistically significant increase for risk among talc</p> <p>21 users; right?</p> <p>22 A. Yes. We're in the same paragraph. Right?</p> <p>23 Q. Yes, Doctor. Thank you.</p> <p>24 A. Yes.</p> <p>25 Q. But you did not know in this paragraph, or</p>	<p>1 Q. Okay. And, again, here you do not report --</p> <p>2 let me start over.</p> <p>3 The association for talc users before 2014</p> <p>4 date was not statistically significant; correct?</p> <p>5 MS. PARFITT: Objection. Form.</p> <p>6 THE WITNESS: Yes. The -- the odds</p> <p>7 ratio was elevated but not statistically significant.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. And you don't call that out in your report,</p> <p>10 do you?</p> <p>11 MS. PARFITT: Objection. Form.</p> <p>12 THE WITNESS: No. It's as it's</p> <p>13 written.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. And as it's written, it says, "The</p> <p>16 association was attenuated but not eliminated."</p> <p>17 That's the wording you used; correct?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. But if the association is not</p> <p>20 statistically significant, would you still refer to</p> <p>21 that association as attenuated and not eliminated? Is</p> <p>22 that the proper way to refer to it?</p> <p>23 A. If the association was eliminated, if there</p> <p>24 was no association, we would have had an odds ratio of</p> <p>25 1. We have an odds ratio of 1.19.</p>

34 (Pages 130 to 133)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 134	Page 136
<p>1 It is -- I acknowledge that it was not 2 statistically significant, but it was not eliminated. 3 It was attenuated. I think that my statement in my 4 report is accurate.</p> <p>5 Q. So for any epidemiologic study that has an 6 odds ratio that crosses 1 but is reported to be above 7 1 with the odds ratio crossing 1 -- do you understand 8 what I'm asking? -- would you refer to that as an 9 association, an null association, a not statistically 10 significant association? What terminology would you 11 use?</p> <p>12 A. I would refer to it as a non-statistically 13 significant association. If the data show 19 percent 14 increased risk, it's not statistically significant.</p> <p>15 Q. And by saying that, what you're saying is 16 that the odds ratio that -- could fall with any -- 17 within the range identified; correct?</p> <p>18 MS. PARFITT: Objection. Form.</p> <p>19 THE WITNESS: The -- when you report a 20 95 percent confidence interval, it gives a range of 21 values which is statistically compatible with what you 22 found. Like, if the study were repeated again with 23 other samples, you might find an odds ratio that was a 24 bit higher or a bit lower.</p> <p>25 But I think that it's very important to make</p>	<p>1 with respect to talc?</p> <p>2 A. If you -- I know you have it right in front 3 of you. So if I could see it, so I could report it 4 accurately. I think I know what I found, but that was 5 paper that was done ten years ago.</p> <p>6 MR. JAMES: Okay. And, Dr. Moorman, 7 I'm marking as Exhibit 16 a paper entitled "Ovarian 8 Cancer Risk Factors in African-American and White 9 Women."</p> <p>10 I'm handing you two copies to pass along. 11 (Exhibit No. 16 was marked for identification.)</p> <p>12 THE WITNESS: Okay. So we reported on 13 talc use for white women and for African-American 14 women. Neither association was statistically 15 significant, again, particularly for the African 16 American, which can be a reflection of the relatively 17 small sample size for African-American women. It was 18 an odds ratio of 1.19; in the white women, it was 19 1.04.</p> <p>20 BY MR. JAMES:</p> <p>21 Q. And those two associations reported in your 22 paper in 2009 are not reported in your report, are 23 they?</p> <p>24 A. I did not -- I do not believe that I reported 25 those specific odds ratios. Data from the</p>
Page 135	Page 137
<p>1 the distinction between no association and no 2 statistically significant association.</p> <p>3 BY MR. JAMES:</p> <p>4 Q. But you didn't make that distinction in your 5 report?</p> <p>6 MS. PARFITT: Objection.</p> <p>7 THE WITNESS: You've asked the 8 question, and I've acknowledged that I did not address 9 statistical significance in that sentence.</p> <p>10 BY MR. JAMES:</p> <p>11 Q. On the same page of your report, if we go 12 back to page 5, you refer to a 2009 paper entitled 13 "Ovarian Cancer Risk Factors in African-American and 14 White Women"; correct?</p> <p>15 A. Let me get to page 5. Which paragraph are 16 you --</p> <p>17 Q. So it's the second paragraph. In fact, you 18 refer to it here as the North Carolina Ovarian Cancer 19 Study; correct?</p> <p>20 A. Right. Right. Okay. Yes.</p> <p>21 Q. My apologies. I -- with -- in conjunction 22 that study, you published a paper in 2009; correct?</p> <p>23 A. Right. Talc was not the primary focus of it, 24 but it was one of the risk factors that we looked at.</p> <p>25 Q. And do you recall the results of that study</p>	<p>1 North Carolina ovarian cancer study was included in 2 the meta-analyses that I did describe.</p> <p>3 Q. And with respect to odds ratio of 1.04 for 4 white women -- do you see that? Are we looking at the 5 same table together? Table 2?</p> <p>6 A. Yes.</p> <p>7 Q. Okay. And the 1.04 association there is very 8 close to the null; correct?</p> <p>9 MS. PARFITT: Objection. Form.</p> <p>10 THE WITNESS: Yes, it's close to 1.</p> <p>11 BY MR. JAMES:</p> <p>12 Q. And it has the odds ratio that crosses 1; 13 correct? The odds ratio range? Is that a fair way to 14 say it?</p> <p>15 A. No.</p> <p>16 Q. Okay. Tell me how to say it.</p> <p>17 A. The 95 percent confidence interval --</p> <p>18 Q. That's right.</p> <p>19 A. -- does cross 1.</p> <p>20 Q. So we have the 1.04 with the CI crossing 1; 21 correct?</p> <p>22 A. Yes.</p> <p>23 Q. Would you refer to the 1.04 as an association 24 that is attenuated but not eliminated?</p> <p>25 A. Well, first of all, I would not refer to it</p>

35 (Pages 134 to 137)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 138	Page 140
<p>1 as attenuated because that implies that there's a 2 comparison with something else; and in the other 3 paper, it was comparing the full study population to a 4 subset. So I would never refer to this as attenuated. 5 This is what was shown in this particular 6 study. It's an odds ratio of 1.04. It's very close 7 to 1. 8 Q. Fair enough. And fair point about 9 attenuated. 10 Would you refer to a 1.04 with a CI that 11 crosses 1 as a positive association, as professional 12 epidemiologist? 13 A. When I would look at that, I would say that 14 there's little evidence of an association, very close 15 to 1, in this study population -- in this study. 16 Q. You've also published another study coming 17 out of the North Carolina Ovarian Cancer Study; 18 correct? 19 A. I have published quite a few papers that came 20 out of the North Carolina Ovarian Cancer Study. 21 Q. And do you recall publishing a paper in 2010 22 entitled "Primary peritoneal and ovarian cancers: An 23 epidemiologic comparative analysis"? 24 A. I was a coauthor on that paper, yes. 25 Q. Okay. And is this paper discussed in your</p>	<p>1 A. Yes, that's what's reported there based on a 2 quite small sample size. 3 Q. And, again, both of these associations are 4 not statistically significant; correct? 5 A. That is correct. 6 Q. And also I see over here to the left, the 7 category listed here is labeled "Talc use"; correct? 8 A. Yes. 9 Q. So this paper looks specifically at talcum 10 powders; is that right? 11 A. I -- I believe that, in that questionnaire, 12 it was specifically asking about talc use. 13 Q. And, again, the results of this study are not 14 reported in your report; correct? 15 A. As I said before when you asked that, the 16 data from the North Carolina Ovarian Cancer are 17 included in the Terry paper that combined data from 18 multiple studies. 19 Q. On page 11 of your report, Dr. Moorman, you 20 state, in the -- I guess it's the second paragraph 21 down from the top, starting with the "it is important" 22 language. 23 A. Mm-hmm. 24 Q. Okay. And if you look down to the second 25 sentence, you note there that (as read):</p>
Page 139	Page 141
<p>1 expert report at all? 2 A. I don't think that I specifically addressed 3 it. Again, the data from the North Carolina Ovarian 4 Cancer Study was included in the Terry analysis -- 5 MR. JAMES: And I've marked the study 6 that I just referenced as Exhibit No. 17. I'm going 7 to hand you two copies. 8 (Exhibit No. 17 was marked for identification.) 9 BY MR. JAMES: 10 Q. And, Dr. Moorman, if we turn to page 995, 11 there is a Table 2 continued onto page. And if you 12 look down, this paper does report odds ratios for talc 13 use; correct? 14 A. Yes, it does. 15 Q. And for -- if you look over to the right, all 16 the way to the right, you see that you've reported a 17 1.15 not statistically significant association for 18 serous invasive ovarian cancer; correct? 19 A. That's correct. 20 Q. And that's with a CI that crosses 1; correct? 21 A. That is correct. 22 Q. And if you look to the left of that, you've 23 reported here a .76 odds ratio for the relationship 24 between talc use and primary peritoneal cancer; 25 correct?</p>	<p>1 "It is not unusual for scientists 2 and epidemiologists to weigh the 3 Hill factors differently in 4 reaching the conclusion." 5 Correct? 6 A. Yes, I state that. 7 Q. And then in the next sentence, you go on to 8 provide examples of that; correct? 9 A. Correct. 10 Q. And you note there (as read): 11 "The evidence that cigarette 12 smoking causes lung cancer or 13 asbestos causes lung disease." 14 Right? 15 A. Yes. 16 Q. And those are the examples that you're 17 providing to support the prior sentence that 18 epidemiologists can sometimes weigh things 19 differently; is that right? 20 A. I give that as an example, yes. 21 Q. For the two examples that you've provided 22 there, has the medical and scientific community 23 accepted that smoking causes lung cancer and that 24 asbestos causes lung disease? 25 A. I think that, yes, that is true. Now, the</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 142	Page 144
<p>1 point that I am making here is that some scientists, 2 especially in the early years when the data were 3 accumulating related to smoking and lung cancer, some 4 people weighted the evidence differently. 5 For example, some of the studies looked at 6 whether people reported whether or not they inhaled or 7 not, and some funny results were observed there. And 8 some scientists thought that was really important 9 evidence against an association, whereas others 10 thought it was -- it was not to be regarded very 11 seriously. 12 Q. Do you regard the body of evidence on smoking 13 and asbestos to be equivalent to the body of evidence 14 on talc and ovarian cancer with regard to evaluating 15 cause? 16 MS. PARFITT: Objection. 17 THE WITNESS: Could you clarify what 18 you mean by "equivalent"? 19 BY MR. JAMES: 20 Q. Sure. By providing these two examples 21 here -- first, the smoking example, and second, the 22 asbestos example -- are you suggesting that the body 23 of evidence to support the causal conclusion with 24 respect to asbestos and smoking is qualitatively 25 and/or quantitatively the same or similar to the body</p>	<p>1 that the criteria that I applied to come to a 2 conclusion of causality are based on strong data. 3 MR. JAMES: Object to the nonresponsive 4 answer. 5 THE WITNESS: Maybe you can clarify 6 your question, because I'm -- maybe I didn't 7 understand what you were asking. 8 BY MR. JAMES: 9 Q. Sure. Dr. Moorman, you provided these 10 examples in your report; correct? 11 A. These are examples to make the point that, as 12 we have said here, that some people weigh different 13 parts of the evidence a bit differently. 14 Q. And so if someone who's reading your report 15 gets an impression that you are equating the body of 16 scientific and medical evidence on the issue of 17 smoking and lung cancer to the body of scientific 18 evidence on talc and ovarian cancer, then they would 19 be getting the wrong impression; is that correct? 20 MS. PARFITT: Objection. 21 THE WITNESS: I don't think that I am 22 equating the evidence for the two. I am -- equating 23 the evidence for the two types of cancer. I was using 24 that to illustrate -- to support the sentence right 25 before that, is that, when we look at these Hill</p>
Page 143	Page 145
<p>1 of evidence we have in 2019 as to talc and ovarian 2 cancer? 3 A. To say that it is the same is -- I don't know 4 that you can say that it's the same. It's different 5 studies done in different time frames. The assessment 6 of the exposure is a bit different. 7 So there are similarities and, you know, the 8 criteria that I applied to come to my conclusion of 9 causality, I think, are similar to what has been 10 applied to smoking and lung cancer. But the data are 11 different. There are different studies, different 12 time frame. 13 Q. Would you say that the data on smoking and 14 lung cancer is stronger than the data on talc and 15 ovarian cancer -- 16 MS. PARFITT: Objection. 17 BY MR. JAMES: 18 Q. -- to support a causal conclusion? 19 A. I'm not sure why one would make such a 20 comparison of what is stronger or not. I mean, 21 clearly, we know that smoking and lung cancer is one 22 of the strongest associations between an exposure and 23 a cancer. 24 The odds ratio that is associated with talc 25 use and ovarian cancer is not as large, but I think</p>	<p>1 factors, scientists can look at them and they might 2 weight one more heavily than another. 3 BY MR. JAMES: 4 Q. And you -- you believe that the medical 5 community accepts that smoking is a cause of lung 6 cancer; correct? 7 A. Yes, in general, I think that's true. 8 Q. Does the medical community believe that talc 9 is a cause of ovarian cancer? Is that the medical 10 community's consensus? 11 MS. PARFITT: Objection. Form. 12 THE WITNESS: I'm not sure who you mean 13 by "the medical community." I -- I think that there 14 are certainly -- there's plenty of evidence to support 15 my conclusion. We have evidence very recently from 16 Health Canada that they have come to the same 17 conclusion. So... 18 BY MR. JAMES: 19 Q. Did Health Canada come to a causal 20 conclusion? 21 A. That was my reading of their document. 22 Q. When's the last time you've read the 23 documents from Health Canada? 24 A. Probably within the last few days. 25 Q. Did Plaintiffs' counsel provide those to you?</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 146	Page 148
<p>1 A. Yes, they did.</p> <p>2 Q. Okay. And your recollection is that the</p> <p>3 Health Canada documents state that talc is a cause of</p> <p>4 ovarian cancer?</p> <p>5 A. I definitely recall them using the "causal"</p> <p>6 language in the document. If -- we can pull it up if</p> <p>7 we want to confirm the precise language.</p> <p>8 Q. Other than identifying Health Canada, which</p> <p>9 you've just done, are there any other bodies or</p> <p>10 scientific organizations or medical organizations that</p> <p>11 you can cite to that have concluded that talc is a</p> <p>12 cause of ovarian cancer?</p> <p>13 A. We've already discussed the IARC conclusion</p> <p>14 that it's possibly carcinogenic.</p> <p>15 Q. And so, again, I'm asking you about -- sorry.</p> <p>16 A. Sorry. Go ahead.</p> <p>17 Q. Sorry. My apologies.</p> <p>18 A. Okay.</p> <p>19 Q. Were you done?</p> <p>20 A. I'm finished.</p> <p>21 Q. So my question, I think, is different than</p> <p>22 that the one you're answering.</p> <p>23 A. Yeah.</p> <p>24 Q. So I'm asking you if you're aware of any</p> <p>25 scientific or medical bodies that have concluded that</p>	<p>1 ovarian cancer. So...</p> <p>2 Q. And when you say talc -- sorry. I think</p> <p>3 you're dropping off a bit, and so I'm jumping in too</p> <p>4 quickly. And I apologize.</p> <p>5 Are you done?</p> <p>6 A. I'm finished, yes.</p> <p>7 Q. You're referring there to a journal article;</p> <p>8 is that right?</p> <p>9 A. It was a summary of -- I think it was</p> <p>10 something like "What's new in ovarian cancer." It was</p> <p>11 published maybe --</p> <p>12 Q. And do you believe the article that you're</p> <p>13 referring to represents the consensus view of the</p> <p>14 medical community?</p> <p>15 MS. PARFITT: Objection. Form.</p> <p>16 THE WITNESS: I don't know that it does</p> <p>17 or not. It wasn't presented as the official opinion</p> <p>18 of that organization.</p> <p>19 BY MR. JAMES:</p> <p>20 Q. And the article that you were mentioning, you</p> <p>21 said increased risk -- or increased association. Is</p> <p>22 that what you said? I don't have the realtime in</p> <p>23 front of me right now.</p> <p>24 A. I don't have it in front of me either.</p> <p>25 Q. Okay.</p>
Page 147	Page 149
<p>1 talc is a general cause of ovarian cancer.</p> <p>2 A. I'm not aware of a -- I'm not aware of a</p> <p>3 statement that has been published, other than the ones</p> <p>4 that I mentioned.</p> <p>5 Q. And by others that you mentioned, you're</p> <p>6 referring to the Health Canada document?</p> <p>7 A. Yes.</p> <p>8 Q. Okay. And we will turn back to that, and</p> <p>9 that way we can have a copy in front of us both.</p> <p>10 Okay?</p> <p>11 A. Okay.</p> <p>12 Q. With regard to IARC, again, you understand</p> <p>13 that they have concluded "possible." Correct?</p> <p>14 A. They conclude possible at that point in time,</p> <p>15 which was 2010.</p> <p>16 Q. Have you ever looked to see if any medical</p> <p>17 organizations that represent the gynecologic oncology</p> <p>18 community have concluded that talc is a cause of</p> <p>19 ovarian cancer?</p> <p>20 A. I am aware that, in a recent article in</p> <p>21 Obstetrics and Gynecology, which is one of the leading</p> <p>22 journals in the field, they were summarizing some of</p> <p>23 the information that is new. They were describing the</p> <p>24 Penninkilampi meta-analysis, and their conclusion was</p> <p>25 that talc is associated with increased risk for</p>	<p>1 A. I am recalling something like there is --</p> <p>2 I don't know what the phrasing was. It's associated</p> <p>3 with increased risk or there is an increased risk of</p> <p>4 ovarian cancer with talc use.</p> <p>5 Q. Do you recall if that article made a</p> <p>6 statement on causality?</p> <p>7 A. I don't recall.</p> <p>8 Q. Have you consulted information provided by</p> <p>9 the ACOG or the SGO with respect to the talc ovarian</p> <p>10 cancer hypothesis?</p> <p>11 MS. PARFITT: Objection.</p> <p>12 THE WITNESS: I don't recall if I have</p> <p>13 or not.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. Would you be interested to know the positions</p> <p>16 by the leading organizations for the gynecologic</p> <p>17 oncology community on this issue?</p> <p>18 MS. PARFITT: Objection. Form.</p> <p>19 THE WITNESS: Of course. Any</p> <p>20 information is important to know.</p> <p>21 MR. JAMES: I'm going to mark as</p> <p>22 Exhibit No. 18 a copy of a statement issued by ACOG on</p> <p>23 talc use and ovarian cancer.</p> <p>24 (Exhibit No. 18 was marked for identification.)</p> <p>25 MR. JAMES: I'm handing you two copies</p>

38 (Pages 146 to 149)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 150	Page 152
<p>1 again.</p> <p>2 BY MR. JAMES:</p> <p>3 Q. Dr. Moorman, have you seen this statement</p> <p>4 before?</p> <p>5 A. I don't recall if I have or not. I might</p> <p>6 have.</p> <p>7 Q. Do you see at the bottom of the statement --</p> <p>8 it's a single paragraph -- the statement concludes</p> <p>9 with the quote (as read):</p> <p>10 "There was no medical consensus</p> <p>11 that talcum powder causes ovarian</p> <p>12 cancer."</p> <p>13 Do you see where I was reading?</p> <p>14 A. I do see that.</p> <p>15 Q. Do you disagree with that statement?</p> <p>16 A. Again, going back to the recent conclusion</p> <p>17 from Health Canada, I think that that is some evidence</p> <p>18 of medical consensus. And I do acknowledge that</p> <p>19 this -- what is said here, that -- yeah, I acknowledge</p> <p>20 what they have written here, yes.</p> <p>21 Q. Have you, in preparing your report for this</p> <p>22 litigation, have you taken a look to see what the</p> <p>23 National Cancer Institute has said about the purported</p> <p>24 association between talc and ovarian cancer?</p> <p>25 A. Yes, I have.</p>	<p>1 inadequate evidence of an association?</p> <p>2 A. Yes.</p> <p>3 And if I may address this document --</p> <p>4 Q. If you could give me just one second, and</p> <p>5 then --</p> <p>6 A. Okay.</p> <p>7 Q. -- I'll let you finish, if you don't mind.</p> <p>8 A. Okay.</p> <p>9 Q. Have you considered this before?</p> <p>10 A. Have I --</p> <p>11 MS. PARFITT: Objection.</p> <p>12 BY MR. JAMES:</p> <p>13 Q. Yes.</p> <p>14 A. -- considered it?</p> <p>15 Q. In forming your opinions in this case?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. It's not cited or discussed in your</p> <p>18 report, is it?</p> <p>19 A. I don't know that I have, but again, it's one</p> <p>20 of the documents that I have -- I have seen in my --</p> <p>21 in my work.</p> <p>22 Q. And so within your report, you do discuss</p> <p>23 findings of IARC; correct?</p> <p>24 A. Yes.</p> <p>25 Q. But you don't discuss findings of the NCI; is</p>
Page 151	Page 153
<p>1 Q. Okay. And what do they say?</p> <p>2 A. I -- when you are -- I think you are</p> <p>3 referring to the PDQ --</p> <p>4 Q. Yes.</p> <p>5 A. -- from NCI.</p> <p>6 Q. Would you like a copy of it?</p> <p>7 A. I would very much like a copy.</p> <p>8 Q. Fair enough.</p> <p>9 Okay. Dr. Moorman, I'm going to hand you a</p> <p>10 copy of the NCI PDQ on "Ovarian, Fallopian Tube, and</p> <p>11 Primary Peritoneal Cancer, Health Professional</p> <p>12 Version."</p> <p>13 (Exhibit No. 19 was marked for identification.)</p> <p>14 THE WITNESS: Thank you.</p> <p>15 BY MR. JAMES:</p> <p>16 Q. And if you turn to -- this is not paginated,</p> <p>17 unfortunately -- have you gotten there already? Or</p> <p>18 I can count for us. I flipped seven times to get</p> <p>19 there. Looks like you beat me to it.</p> <p>20 A. Okay.</p> <p>21 Q. And do you see here that is this the PDQ you</p> <p>22 were thinking of, Dr. Moorman?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. And in here, do you see that the NCI</p> <p>25 has listed perineal talc exposure as a factor with</p>	<p>1 that right?</p> <p>2 A. I don't think that I specifically addressed</p> <p>3 it.</p> <p>4 Q. Is that because it conflicts with your</p> <p>5 litigation opinion?</p> <p>6 MS. PARFITT: Objection.</p> <p>7 THE WITNESS: No.</p> <p>8 May I ask --</p> <p>9 BY MR. JAMES:</p> <p>10 Q. And, Dr. Moorman, you said you wanted to</p> <p>11 comment, and now is fine.</p> <p>12 A. Let's see. I wanted -- when did you print</p> <p>13 out this version of the PDQ, if I may ask you?</p> <p>14 Q. So do you understand that this is a -- this</p> <p>15 is a -- well, if you turn to the back page of the copy</p> <p>16 that I handed you --</p> <p>17 A. Mm-hmm.</p> <p>18 Q. -- the very back --</p> <p>19 A. Okay.</p> <p>20 Q. -- it says "Updated: December 21, 2018."</p> <p>21 A. Okay.</p> <p>22 Q. All the way on the back page.</p> <p>23 A. Yeah.</p> <p>24 Q. Got it.</p> <p>25 A. Okay. One of the -- I have looked at this</p>

39 (Pages 150 to 153)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 154</p> <p>1 very recently, and on the online version, there were 2 some rather what I considered kind of interesting 3 conclusions that were made. I'm actually not seeing 4 it in this version here. But, for example, they -- 5 I'm sorry. I don't see it even mentioned here. 6 But on the online version, they had listed 7 DMPA -- depot medroxyprogesterone acetate -- as 8 something that there was adequate evidence of reduced 9 effect. And they were basing that -- there are very 10 few studies on that to begin with, and as they 11 summarized it, again, the last time I looked at it 12 online, they said it was inconsistent data, but they 13 still summarized that there was adequate evidence. 14 And then in regard to things like comparing 15 the evidence for something like breastfeeding, they 16 said (as read): 17 "Based on solid evidence, 18 breastfeeding is associated with 19 decreased risk of ovarian cancer." 20 If we compare the evidence to breastfeeding 21 to the evidence for talcum -- talc use, again, the 22 online version that I last looked at, it gave a little 23 bit more detail about the meta-analyses and so on. 24 So the meta-analyses for breastfeeding and 25 the meta-analyses for talc, there were a lot of</p>	<p style="text-align: right;">Page 156</p> <p>1 with the NCI? 2 A. Okay. Just looking at this, and it came 3 up -- it says "with inadequate evidence of an 4 association." 5 Did you say "adequate" or "inadequate"? 6 Q. I said "inadequate." 7 A. Okay. My judgment based on the evidence is 8 that there is adequate evidence. So I would disagree 9 with the NCI in the conclusion that they reached. 10 Q. With regard to your discussion that we've had 11 just now on the body of evidence to look at 12 breastfeeding and ovarian cancer risk -- 13 A. Yes. 14 Q. -- and this is a yes-or-no question -- did 15 you conduct a comprehensive review of the scientific 16 medical literature and evidence surrounding the 17 association between breastfeeding and ovarian cancer? 18 A. I did not do as comprehensive a review of 19 that literature as I did for the talc. 20 Q. And have you, in the course of your career, 21 ever looked comprehensively at the body of scientific 22 and medical evidence surrounding the association of 23 breastfeeding and ovarian cancer to the cell studies, 24 the plausibility, the dose-response, have you done all 25 of that with respect to breastfeeding and ovarian</p>
<p style="text-align: right;">Page 155</p> <p>1 similarities. There are roughly 30 studies addressing 2 each of them. For breastfeeding, it's about a 3 25 percent reduction in risk; for talc, about a 4 25 percent increased risk. 5 When you look at the overall number of 6 studies, roughly 90 percent of them support 7 breastfeeding -- in terms of just looking at the 8 direction of the effect -- about 90 percent of them 9 support that breastfeeding is associated with reduced 10 risk. When you look at the meta-analyses for talc, 11 about 90 percent of the studies have an odds ratio 12 greater than 1. 13 And so when we look at the overall body of 14 evidence, to me, I think it's comparable for 15 breastfeeding versus talc, but they conclude that the 16 evidence is adequate for breastfeeding but not 17 adequate for talc. And they don't really describe 18 their methodology for how they reach their 19 conclusions. 20 So it leaves me just a little bit baffled 21 about why is one adequate evidence and one inadequate 22 evidence. 23 Q. If the NCI's PDQ that's available on their 24 website as of today classifies talc as a factor with 25 inadequate evidence of an association, do you disagree</p>	<p style="text-align: right;">Page 157</p> <p>1 cancer? 2 A. I -- in the course of looking at ovarian 3 cancer, I have actually never written a paper that was 4 strictly focused on breastfeeding and ovarian cancer, 5 and that is typically where one would go through the 6 very comprehensive review. 7 I am familiar with much of the literature, 8 but the degree to which I reviewed the literature was 9 not in the same level of detail as I did the talc 10 literature. 11 Q. And do you know if the scientists at the NCI 12 who have commented on the association between 13 breastfeeding and ovarian cancer have conducted an 14 examination of the scientific and medical literature 15 that is more comprehensive, less comprehensive, or the 16 same that you've conducted? 17 MS. PARFITT: Objection to form. 18 THE WITNESS: They do not describe 19 their methodology, and so I can't say if it was more 20 or less comprehensive. 21 BY MR. JAMES: 22 Q. Okay. Dr. Moorman, on page 10 of your 23 report -- 24 A. Yes. 25 Q. -- you have the -- it's the third full</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 158	Page 160
<p>1 paragraph down, and you make the statement that</p> <p>2 meta-analyses are "considered to be some of the</p> <p>3 strongest evidence for a causal association."</p> <p>4 Do you see where I'm reading that?</p> <p>5 A. Yes, I do.</p> <p>6 Q. Okay. So that's -- so you've made that</p> <p>7 comment.</p> <p>8 And then further down, you say (as read):</p> <p>9 "Data from meta-analyses are</p> <p>10 particularly important for</p> <p>11 evaluating exposure-disease</p> <p>12 relationships such as talc and</p> <p>13 ovarian cancer where the relative</p> <p>14 risks for most individuals are</p> <p>15 approximately 1.2 to 1.5."</p> <p>16 Do you see where I've read that?</p> <p>17 A. Yes, I do.</p> <p>18 Q. Can you cite any published authority for the</p> <p>19 statement that meta-analyses are considered to be some</p> <p>20 of the strongest evidence for causal association?</p> <p>21 A. I'm trying to think of whether it's a</p> <p>22 published source. It's something that I have seen,</p> <p>23 for example, multiple times in lectures and so on</p> <p>24 where it will give a hierarchy of evidence. And</p> <p>25 meta-analyses combining data from multiple studies is</p>	<p>1 data as reported. It could not correct the bias.</p> <p>2 Q. So to the extent the meta-analyses are</p> <p>3 collecting data from underlying studies that are</p> <p>4 flawed by recall bias or confounding, those</p> <p>5 inaccuracies carry over into the meta-analyses;</p> <p>6 correct?</p> <p>7 MS. PARFITT: Objection.</p> <p>8 THE WITNESS: I would not characterize</p> <p>9 it as "carry over." We recognize when we combine the</p> <p>10 data from the meta-analyses, it is combining the</p> <p>11 reported data. If there were biases that either led</p> <p>12 to an underestimate or an overestimate of the relative</p> <p>13 risk, they are not correcting that.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. And do you caution the reader of your MDL</p> <p>16 report about that limitation to meta-analyses anywhere</p> <p>17 in your report?</p> <p>18 A. I do not specifically make that caution, no.</p> <p>19 Q. The meta-analyses that we have on the talc</p> <p>20 ovarian cancer issue, they are progressed over a</p> <p>21 period of time; correct?</p> <p>22 A. That is correct.</p> <p>23 Q. And we know that there's been two recent</p> <p>24 meta-analyses. And all of the meta-analyses that have</p> <p>25 been published on this association are in some ways</p>
Page 159	Page 161
<p>1 often put at kind of the top of the pyramid for making</p> <p>2 causal assessments.</p> <p>3 I want to say that maybe some of the</p> <p>4 evidence-based medicine -- I know that there are</p> <p>5 online summaries of evidence-based medicine that would</p> <p>6 describe meta-analyses as kind of some of the</p> <p>7 strongest evidence for causality.</p> <p>8 Q. Meta-analyses combine data from underlying</p> <p>9 studies; correct?</p> <p>10 A. That is correct.</p> <p>11 Q. Meta-analyses do not correct for bias and</p> <p>12 confounding in underlying studies; correct?</p> <p>13 A. The meta-analysis itself -- no. They combine</p> <p>14 the data. They...</p> <p>15 Q. And -- were you finished?</p> <p>16 A. Yeah. They do not correct for the bias.</p> <p>17 Q. Meta-analyses, for example, do not eliminate</p> <p>18 recall bias if there is a recall bias problem in the</p> <p>19 underlying studies; correct?</p> <p>20 A. That is correct. Meta-analyses cannot do</p> <p>21 that.</p> <p>22 Q. And the meta-analyses studies that you</p> <p>23 reviewed and discussed in your report all concede that</p> <p>24 point, don't they?</p> <p>25 A. They acknowledge that they are combining the</p>	<p>1 overlapping; correct?</p> <p>2 MS. PARFITT: Objection to form.</p> <p>3 THE WITNESS: The meta-analyses, their</p> <p>4 intent is to combine all the published data. So, yes,</p> <p>5 there is some overlap. More recent ones would have</p> <p>6 included studies that had been published in prior</p> <p>7 meta-analyses.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. And recognizing that meta-analyses can differ</p> <p>10 here and there for various -- various reasons, the</p> <p>11 talc ovarian cancer meta-analyses generally pull data</p> <p>12 from the same body of literature; is that fair?</p> <p>13 A. Yes.</p> <p>14 Q. And any suggestion that because you have</p> <p>15 multiple meta-analyses reaching around the same odds</p> <p>16 ratio and that that somehow demonstrates consistency,</p> <p>17 isn't that a little bit misleading?</p> <p>18 MS. PARFITT: Objection. Form.</p> <p>19 THE WITNESS: I think that when we look</p> <p>20 at it, when we see that, early on, you see some</p> <p>21 meta-analyses were done, I want to say maybe in the</p> <p>22 '90s, and then as more data are added in, you -- they</p> <p>23 still settled in on roughly the same summary odds</p> <p>24 ratio as even more data were accumulated.</p> <p>25 Sometimes there is a concern that early on</p>

41 (Pages 158 to 161)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 162	Page 164
<p>1 the studies with positive associations are published, 2 and then after -- as time goes on, other studies are 3 done that didn't find that association. So you would 4 expect that the summary odds ratio might become 5 attenuated as more studies were added. 6 And that's not the situation with the talc 7 literature. It's been pretty consistent from the 8 meta-analyses done in the 1990s to the 2000s to 2018. 9 BY MR. JAMES: 10 Q. And the 2018 meta-analyses that they are 11 grabbing in the studies from decades prior, they're 12 grabbing in the same studies that the 1990s 13 meta-analyses grabbed in; right? 14 MS. PARFITT: Objection. Form. 15 THE WITNESS: Yeah. The purpose is to 16 include all of the published data. So yes, of course. 17 BY MR. JAMES: 18 Q. And in your report, you place significant 19 emphasis -- if that's a fair word -- on meta-analyses. 20 Is that a fair way to describe it? 21 MS. PARFITT: Objection. 22 THE WITNESS: Yes, I think I -- I think 23 that's fair to characterize it that way. 24 BY MR. JAMES: 25 Q. You -- did you read the conclusions of all of</p>	<p>1 opportunity to ask questions afterwards. 2 A. Some of them did raise some concerns about 3 whether or not it could be a causal association. 4 Q. We're going to take a look at the studies 5 shortly as I grab these folders out. 6 Did you report in your report for the MDL 7 any of the cautionary language from these 8 meta-analyses about causation? 9 A. I -- in my report, when you look at some of 10 the cautionary language, they will refer to perhaps 11 concerns about recall bias or things like that. 12 In my report, I went through potential 13 biases and how I weighed that and whether I thought it 14 was an important concern in the studies that 15 contributed to the meta-analyses. 16 Q. Did you talk about any weaknesses or problems 17 with the meta-analyses themselves? 18 A. I don't believe I did in my report. 19 Q. And just -- okay. 20 MR. JAMES: I'm going to mark as 21 Exhibit No. 20 a meta-analysis that I think that 22 you've mentioned this morning. It's the Penninkilampi 23 study. 24 THE WITNESS: Yes. 25 MR. JAMES: I'm going to hand you two</p>
Page 163	Page 165
<p>1 the meta-analyses performed to date? 2 A. I did. 3 Q. Do any of the authors of the meta-analyses 4 performed to date conclude causation? 5 A. If I may take a minute to address the issue 6 of how causation is reported in the epidemiologic 7 literature. 8 Q. With all due respect, Doctor, if you could 9 just answer the question. 10 A. I think that they typically refer to, like, 11 increased risk. I don't know that any of them refer 12 to -- made the conclusion of -- I don't know that they 13 used the word "causal." 14 Q. In fact, many of the meta-analyses 15 specifically caution against a causal interpretation, 16 don't they? 17 MS. PARFITT: Objection. 18 THE WITNESS: Once again, if -- may 19 I take a moment to address how the word -- 20 BY MR. JAMES: 21 Q. Because my time is limited -- 22 A. Okay. 23 Q. -- I'm really going to have to respectfully 24 ask you to answer my question to the extent that 25 you're able, and then your counsel will have an</p>	<p>1 copies again. 2 (Exhibit No. 20 was marked for identification.) 3 MR. JAMES: It's marked as Exhibit 20. 4 THE WITNESS: Would this be a good time 5 to take a break before we get into -- 6 MR. JAMES: Absolutely. 7 THE WITNESS: Okay. 8 THE VIDEOGRAPHER: Going off record at 9 1:48 p.m. 10 (Recess taken from 1:48 p.m. to 2:03 p.m.) 11 THE VIDEOGRAPHER: Back on record at 12 2:03 p.m. 13 BY MR. JAMES: 14 Q. Dr. Moorman, I handed you had a copy of the 15 Penninkilampi paper. 16 A. I'm sorry, the papers were moved while 17 I was... 18 Q. It was marked as Exhibit 20, I believe. 19 Here, I have an extra, if that would speed 20 things along. I'm sure it's somewhere in there. 21 A. It got moved around. Oh, here it is. 22 Q. Okay. Again, Dr. Moorman, this is one of the 23 meta-analyses that you reviewed to inform your 24 opinions in this case; correct? 25 A. That is correct.</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 166</p> <p>1 Q. It's also one of the more recent 2 meta-analyses on the issue; correct? 3 A. That's correct. 4 Q. And what did the Penninkilampi authors say 5 about causation? 6 A. Okay. They describe perineal talc is 7 associated with a 24 to 39 percent increased risk of 8 ovarian cancer. 9 And this is a very typical way that it would 10 be described in the epidemiologic literature. It -- 11 as described very eloquently in some articles in the 12 American Journal of Public Health last spring, they 13 noted that, to the detriment of the science, that 14 epidemiologists are frequently loathe -- or don't 15 often use the word "causal" when they describe a risk 16 factor; and, in part, this is because we are relying 17 on observational data. This is not an experimental 18 study. 19 And so, many times, reviewers, if they refer 20 to "we found that talc caused ovarian cancer," they 21 would object to that, saying that it wasn't a 22 randomized controlled trial. 23 But in this series of articles in the 24 American Journal of Public Health, they indicated that 25 the tendency not to use the word "causal" is to the</p>	<p style="text-align: right;">Page 168</p> <p>1 "Hence, while perineal talc use 2 has not been shown to be safe, in 3 a similar regard, a certain causal 4 link between talc use and ovarian 5 cancer has not yet been 6 established." 7 That's what the authors say; correct? 8 A. That's what they say, yes. 9 Q. Okay. So they caution that causation has not 10 been established; correct? 11 MS. PARFITT: Objection. 12 THE WITNESS: They say a certain causal 13 link has not been established -- not yet been 14 established. 15 BY MR. JAMES: 16 Q. And you're here today testifying about what 17 you believe to be evidence supporting the causal link; 18 correct? 19 A. Yes, I am -- I am. 20 Q. Okay. And so where in your report do you 21 advise the reader that the Penninkilampi authors 22 expressed reservations about causation? 23 A. I do not have anything like that in my 24 report. 25 MR. JAMES: The next meta-analysis that</p>
<p style="text-align: right;">Page 167</p> <p>1 detriment of the science. It's like "Why would we be 2 looking at risk factors for a disease if we didn't 3 think that it caused the disease?" 4 So I think that when an epidemiologist sees 5 an increased risk of ovarian cancer, we are thinking 6 that this is -- this causes ovarian cancer. 7 Q. But epidemiologists, including many of the 8 meta-analyses that we're about to review, have talked 9 about cause, haven't they? 10 MS. PARFITT: Objection. 11 THE WITNESS: Some of them have 12 addressed, yes. 13 BY MR. JAMES: 14 Q. For example, Penninkilampi doesn't seem shy 15 of the word "cause." If we look at page 42, 16 Dr. Moorman, we see, in the top paragraph in the 17 left-hand column, at the bottom of that paragraph, the 18 Penninkilampi authors write, quote -- this is the last 19 sentence -- 20 A. Wait. Page 42? 21 Q. Page 42. 22 A. Yes. 23 Q. It's the top left paragraph. The bottom last 24 sentence of that paragraph, the authors state 25 (as read):</p>	<p style="text-align: right;">Page 169</p> <p>1 we can look at is the Berg -- or Berge meta-analysis. 2 I'm going to mark that as Exhibit 21. 3 (Exhibit No. 21 was marked for identification.) 4 BY MR. JAMES: 5 Q. Do the Berge authors conclude that the 6 evidence is sufficient to support a causation 7 conclusion? 8 A. They do not make that conclusion, no. 9 Q. In fact, they actually -- they do address 10 causation, don't they? 11 A. They state their opinion, yes. 12 Q. Okay. And their opinion is expressed several 13 times throughout the article. The first is in the 14 abstract of the article; correct? 15 If we look at the abstract, it's the first 16 page of the article, page 248, the last sentence of 17 the abstract. Do you see that? 18 A. Yes, I do. 19 Q. They say (as read): 20 "The heterogeneity of results by 21 study design, however, detracts 22 from a causal interpretation of 23 this association." 24 Correct? 25 A. That's what it says, yes.</p>

43 (Pages 166 to 169)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 170	Page 172
<p>1 Q. Where do you advise the reader of your MDL</p> <p>2 report that the authors of the Berge meta-analyses</p> <p>3 expressed reservations about causation?</p> <p>4 MS. PARFITT: Objection. Form.</p> <p>5 THE WITNESS: That is not in my report.</p> <p>6 BY MR. JAMES:</p> <p>7 Q. Do you see at the very the end of article, at</p> <p>8 the very last page on 256, before the acknowledgment</p> <p>9 section, again, the authors conclude the article with</p> <p>10 a statement that the results (as read):</p> <p>11 "do not support a causal</p> <p>12 interpretation of the</p> <p>13 association."</p> <p>14 Do you see where I'm reading?</p> <p>15 A. They say some -- several aspects of the</p> <p>16 results there.</p> <p>17 Q. Fair enough.</p> <p>18 A. Yes.</p> <p>19 Q. So let's just read the sentence in full. So</p> <p>20 they say (as read):</p> <p>21 "Several aspects of our results,</p> <p>22 including the heterogeneity of</p> <p>23 results between case-control and</p> <p>24 cohort studies, however, do not</p> <p>25 support a causal interpretation of</p>	<p>1 MR. JAMES: And I'm going to reserve</p> <p>2 the time that it takes --</p> <p>3 MS. PARFITT: No, you're not going to</p> <p>4 reserve the time. You asked her a question; she was</p> <p>5 answering it.</p> <p>6 MR. JAMES: It was a yes-or-no</p> <p>7 question.</p> <p>8 MS. PARFITT: You can object -- it was</p> <p>9 not, Scott. Let's have her finish her statement, and</p> <p>10 you can decide what you want to do it with it. But</p> <p>11 she's going to finish her comment.</p> <p>12 Dr. Moorman, please.</p> <p>13 THE WITNESS: So I think that in my</p> <p>14 report, I did address the aspects of the heterogeneity</p> <p>15 of the results, although I might not specifically have</p> <p>16 addressed -- said anything specifically about the</p> <p>17 limitation of the Berge.</p> <p>18 BY MS. PARFITT:</p> <p>19 Q. Right. So my question, which was very</p> <p>20 precise, is where do you note in your MDL report the</p> <p>21 causation reservations of the Berge authors?</p> <p>22 MS. PARFITT: Objection.</p> <p>23 THE WITNESS: And as I stated before,</p> <p>24 that is not in -- that specific reservations of the</p> <p>25 Berge authors, I do not have that in my -- in my</p>
Page 171	Page 173
<p>1 the association."</p> <p>2 That's what they say; correct?</p> <p>3 A. Right.</p> <p>4 Q. And, again, do you advise the readers of your</p> <p>5 MDL report that those are the conclusions of the Berge</p> <p>6 meta-analysis?</p> <p>7 MS. PARFITT: Objection. Form.</p> <p>8 THE WITNESS: I do not specifically do</p> <p>9 that. But in my report, I think that I really address</p> <p>10 some of the heterogeneity of the results between</p> <p>11 case-control and cohort studies and why some of the</p> <p>12 differences might be observed and, for example, some</p> <p>13 of the biases in the cohort studies would lead to an</p> <p>14 underestimate of the --</p> <p>15 BY MR. JAMES:</p> <p>16 Q. And, Dr. Moorman --</p> <p>17 MS. PARFITT: Excuse me --</p> <p>18 BY MR. JAMES:</p> <p>19 Q. -- I'm going to ask you questions about that.</p> <p>20 MS. PARFITT: -- Mr. James, she was in</p> <p>21 the middle of her sentence.</p> <p>22 MR. JAMES: I object to the</p> <p>23 nonresponsive portion of her answer.</p> <p>24 MS. PARFITT: You may, but let her</p> <p>25 complete her answer.</p>	<p>1 report.</p> <p>2 BY MS. PARFITT:</p> <p>3 Q. The next meta-analyses is -- and I'm working</p> <p>4 backwards chronologically -- is the Langseth</p> <p>5 meta-analyses.</p> <p>6 Are you familiar with that paper?</p> <p>7 A. Yes, I have seen that paper.</p> <p>8 MR. JAMES: And I'm going to mark the</p> <p>9 Langseth paper as Exhibit No. 23.</p> <p>10 (Exhibit No. 22 was marked for identification.)</p> <p>11 MR. JAMES: I'm handing you two copies.</p> <p>12 MR. DONATH: 23 or 22?</p> <p>13 MS. BRENNAN: 22.</p> <p>14 MR. JAMES: It's 22. So we'll sub</p> <p>15 stickers.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. So Langseth is 22. Did the authors of</p> <p>18 Langseth conclude that causation is shown? Yes or no,</p> <p>19 please.</p> <p>20 A. They -- if I may take just a moment to read</p> <p>21 through it --</p> <p>22 Q. Sure.</p> <p>23 A. -- as it...</p> <p>24 No, they do not.</p> <p>25 Q. And, in fact, the authors do address the</p>

44 (Pages 170 to 173)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 174	Page 176
<p>1 issue of causation on page 359 of the article; 2 correct, under the section "Proposal to research 3 community." 4 Do you see where I am? 5 A. I do see that. 6 Q. Okay. And the authors state (as read): 7 "The current body of experimental 8 and epidemiological evidence is 9 insufficient to establish a causal 10 association between perineal use 11 of talc and ovarian cancer risk." 12 A. That is correct. And, again, noting the date 13 of this paper, 2008. So quite a lot of evidence has 14 emerged since then. And one of the authors on the 15 paper has since concluded that there is sufficient 16 evidence for causality. 17 Q. And you're talking about a paid expert in 18 this case; correct? 19 MS. PARFITT: Objection. 20 THE WITNESS: Dr. Siemiatycki, who's a 21 paid expert, well-respected epidemiologist. 22 BY MR. JAMES: 23 Q. And he's a paid expert in this litigation for 24 the Plaintiffs; correct? 25 MS. PARFITT: Objection.</p>	<p>1 conclude that the evidence was sufficient to support 2 causation? 3 A. No, they did not. 4 Q. Okay. And, in fact, the authors did address 5 causation in their paper in the abstract; correct? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: Yes, they do. 8 BY MR. JAMES: 9 Q. Okay. And at page 195 in the conclusion of 10 the abstract, the authors say (as read): 11 "The available observational data 12 do not support the existence of a 13 causal relationship between 14 perineal talc exposure and 15 increased risk of epithelial 16 ovarian cancer. Selection bias 17 and uncontrolled confounding may 18 account for the positive 19 associations seen in prior 20 epidemiological studies." 21 That's what the authors say; correct? 22 A. That is what these authors say. 23 Q. And did you report to the reader of your MDL 24 report the Huncharek authors' reserved judgment on 25 causation?</p>
Page 175	Page 177
<p>1 THE WITNESS: That is correct. 2 BY MR. JAMES: 3 Q. Where in your report -- and this is a 4 yes-or-no question, or actually it's not "yes" or 5 "no." You tell me if it exists or not. 6 Where in your report do you show to the 7 reader of the report that the Langseth authors 8 reserved judgment on causation? 9 MS. PARFITT: Objection to form. 10 THE WITNESS: I did not specifically 11 include that in my report. 12 BY MR. JAMES: 13 Q. Dr. Moorman, have you reviewed the Huncharek 14 2003 meta-analyses? 15 A. Yes, I have. 16 MR. JAMES: And I'm going to mark the 17 Huncharek 2003 meta-analyses as Exhibit No. 23, and 18 we'll switch stickers at the break. 19 (Exhibit No. 23 was marked for identification.) 20 BY MR. JAMES: 21 Q. I'm handing you two copies, Dr. Moorman. 22 Is this another meta-analysis that you 23 reviewed in forming your opinions in this case? 24 A. Yes, it is. 25 Q. Okay. Did the authors of this meta-analysis</p>	<p>1 MS. PARFITT: Objection. 2 THE WITNESS: As with the other 3 meta-analysis, this is now 16 years old, and I did not 4 specifically report that, but I did consider in my 5 report the biases and uncontrolled confounding that 6 they were concerned about. 7 BY MR. JAMES: 8 Q. Do any of the -- there are a handful of 9 meta-analyses that precede the Huncharek 2003 10 meta-analyses; correct? 11 A. That is correct. 12 Q. Do any of those meta-analyses conclude 13 causation? 14 MS. PARFITT: Objection. Form. 15 THE WITNESS: I don't believe that they 16 do. 17 BY MR. JAMES: 18 Q. And returning back to our discussion on the 19 Langseth meta-analyses, you noted sort of -- when I 20 asked you a question about their conclusions on 21 causation, you noted the timing of the article; 22 correct? 23 A. Yes. 24 Q. You noted that the article was published 25 in --</p>

45 (Pages 174 to 177)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 178	Page 180
<p>1 A. 2008.</p> <p>2 Q. -- 2008?</p> <p>3 A. Yes.</p> <p>4 Q. That is right?</p> <p>5 So is your opinion that the evidence in 2008</p> <p>6 was, in fact, insufficient to support a causal</p> <p>7 conclusion but has now transitioned to a status where</p> <p>8 it is sufficient?</p> <p>9 MS. PARFITT: Objection. Form.</p> <p>10 THE WITNESS: You have asked me that</p> <p>11 question in -- that or a similar question before.</p> <p>12 There is a growing body of evidence.</p> <p>13 I would be hard-pressed to say at what point in time,</p> <p>14 you know, it reached the tipping point where there is</p> <p>15 enough evidence to say that there is this causal</p> <p>16 association.</p> <p>17 At this point in time, I feel very confident</p> <p>18 in saying that, but I can't say when sufficient data</p> <p>19 accumulated to say that. I think that's an impossible</p> <p>20 answer -- or an impossible question to answer.</p> <p>21 BY MR. JAMES:</p> <p>22 Q. And the reason I asked it again is because</p> <p>23 you made the qualification in discussing the Langseth</p> <p>24 paper. When I asked you about the authors'</p> <p>25 conclusions on causation, you specifically noted that</p>	<p>1 A. No --</p> <p>2 MS. PARFITT: Objection.</p> <p>3 THE WITNESS: -- for the same reasons</p> <p>4 I described prior.</p> <p>5 MR. JAMES: And I'm going to mark the</p> <p>6 2013 Terry paper as Exhibit 24.</p> <p>7 (Exhibit No. 24 was marked for identification.)</p> <p>8 MR. JAMES: I think I'm back on track</p> <p>9 on the numbers. I'm handing you two copies.</p> <p>10 BY MR. JAMES:</p> <p>11 Q. And again, Dr. Moorman, you've used this</p> <p>12 paper to inform your opinions in the case; correct?</p> <p>13 A. That is correct.</p> <p>14 Q. And if you look at the last page of the text</p> <p>15 on 820 with me, you see in the last paragraph, which</p> <p>16 is -- the last paragraph on page 820, the authors</p> <p>17 state at the top right-hand column (as read):</p> <p>18 "More work is needed to understand</p> <p>19 how genital powders may exert a</p> <p>20 carcinogenic effect and which</p> <p>21 constituents may be involved."</p> <p>22 Do you see that sentence?</p> <p>23 A. Yes, I do.</p> <p>24 Q. There, the authors are again noting that --</p> <p>25 let me rephrase it this way.</p>
Page 179	Page 181
<p>1 it was a paper from the 2008 time frame; correct?</p> <p>2 A. Right. And I think that -- I think that it</p> <p>3 is obvious that one of the authors, considering all</p> <p>4 the additional data that's accumulated, would -- has</p> <p>5 made a different conclusion at this point in time.</p> <p>6 Q. And the author you're referring to there is</p> <p>7 the author that we were discussing as a paid expert in</p> <p>8 this case; correct?</p> <p>9 MS. PARFITT: Objection. Form.</p> <p>10 THE WITNESS: Yes. We established he</p> <p>11 is a paid expert and, at the same time, a very</p> <p>12 well-respected epidemiologist.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. There's also a pooled analysis that you</p> <p>15 looked at to inform your opinions in this case;</p> <p>16 correct?</p> <p>17 A. Yes.</p> <p>18 Q. Okay. And the pooled analysis is the Terry</p> <p>19 2013 paper?</p> <p>20 A. That is correct.</p> <p>21 Q. Okay. Did the Terry 2013 paper conclude</p> <p>22 cause?</p> <p>23 MS. PARFITT: Objection. Form.</p> <p>24 BY MR. JAMES:</p> <p>25 Q. It's yes or no.</p>	<p>1 The authors there are reserving judgment on</p> <p>2 causation; correct?</p> <p>3 MS. PARFITT: Objection. Form.</p> <p>4 THE WITNESS: I don't think that that</p> <p>5 is how I would necessarily interpret that.</p> <p>6 BY MR. JAMES:</p> <p>7 Q. Okay.</p> <p>8 A. I think that, first of all, basically, any</p> <p>9 scientific paper concludes with "more work is needed."</p> <p>10 And so it's talking about, you know, trying to advance</p> <p>11 scientific knowledge by understanding the biological</p> <p>12 mechanism.</p> <p>13 But I don't see anything -- any statement</p> <p>14 there related to causal. It says "small to moderate</p> <p>15 increased risk of ovarian cancer." And as I've stated</p> <p>16 previously, basically, when we talk about risk</p> <p>17 factors, we are thinking that this is something that</p> <p>18 causes this cancer.</p> <p>19 Q. So in your professional opinion, the word</p> <p>20 "risk factor" is equivalent to "causation"?</p> <p>21 A. Not always equivalent. And if I may give an</p> <p>22 example.</p> <p>23 Women who have higher educational level are</p> <p>24 at increased risk for breast cancer. And so higher</p> <p>25 education level, we might describe it as a risk factor</p>

46 (Pages 178 to 181)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 182	Page 184
<p>1 for breast cancer. But, clearly, going to college is</p> <p>2 not going to cause breast cancer. It's the other</p> <p>3 factors that are associated with it, like your</p> <p>4 childbearing patterns, alcohol use, other things.</p> <p>5 But when we talk about a risk factor and</p> <p>6 there is a plausible biological mechanism to get from</p> <p>7 that exposure to cancer, I think that "risk factor"</p> <p>8 and "cause" are pretty synonymous.</p> <p>9 Q. But to say something is associated in</p> <p>10 epidemiologic literature is not to say that it's</p> <p>11 causal.</p> <p>12 Do you agree with that?</p> <p>13 MS. PARFITT: Objection.</p> <p>14 THE WITNESS: Yes. That's kind of</p> <p>15 epi 101, that everything that is associated is not</p> <p>16 necessarily a cause.</p> <p>17 BY MR. JAMES:</p> <p>18 Q. To reach a causal conclusion, it's -- one</p> <p>19 must undertake a more in-depth analysis; correct?</p> <p>20 A. As I did for this, and as all of us in this</p> <p>21 room are well aware, the Bradford Hill framework is a</p> <p>22 framework for taking the data and leading to making a</p> <p>23 judgment on causality.</p> <p>24 Q. So if a paper refers to something as a risk</p> <p>25 factor or a potential risk factor or a modifiable risk</p>	<p>1 meta-analyses.</p> <p>2 Q. Are you aware of any flaws in the</p> <p>3 Penninkilampi study?</p> <p>4 MS. PARFITT: Objection. Form.</p> <p>5 THE WITNESS: Overall, I felt like it</p> <p>6 seemed to be a very well done meta-analysis. When we</p> <p>7 look at judgments of meta-analyses, we like to see</p> <p>8 things like, you know, what were the search terms they</p> <p>9 used? What were the criteria for including or</p> <p>10 excluding studies? Were the study questions defined</p> <p>11 in advance?</p> <p>12 And when I look through all of that,</p> <p>13 I judged it overall to be a very well done</p> <p>14 meta-analysis.</p> <p>15 BY MR. JAMES:</p> <p>16 Q. And so your answer to the question that</p> <p>17 I asked is no; correct?</p> <p>18 MS. PARFITT: Objection.</p> <p>19 THE WITNESS: I -- I don't see any</p> <p>20 serious problems with any -- you characterized it as</p> <p>21 "flaws." I don't -- I don't see anything that I would</p> <p>22 characterize as a flaw in their methodology.</p> <p>23 BY MR. JAMES:</p> <p>24 Q. If you look at page 47 with me, Dr. Moorman,</p> <p>25 in the "Conclusions" section.</p>
Page 183	Page 185
<p>1 factor, that terminology by itself does not suggest</p> <p>2 that the authors of that paper have concluded</p> <p>3 causation; correct?</p> <p>4 A. I -- I think that I have answered that</p> <p>5 question already.</p> <p>6 When they're -- if they refer to it as a</p> <p>7 risk factor, they may or may not have gone through the</p> <p>8 full Bradford Hill evaluation of it. And then, also,</p> <p>9 some things that we refer to as risk factors, where</p> <p>10 there is not a plausible biological mechanism, we</p> <p>11 wouldn't equate risk factor and cause in that</p> <p>12 situation as well.</p> <p>13 Q. So you -- returning back to the Penninkilampi</p> <p>14 meta-analysis, which I believe will be somewhere in</p> <p>15 that pile --</p> <p>16 A. Mm-hmm.</p> <p>17 Q. -- you cite Penninkilampi 14 times in your</p> <p>18 report.</p> <p>19 Were you aware of that?</p> <p>20 A. I don't know how many times I've cited it.</p> <p>21 Q. It's one of the most cited articles in your</p> <p>22 report.</p> <p>23 Were you aware of that?</p> <p>24 A. I know that I referred to it frequently</p> <p>25 because it is one of the most up-to-date, most recent</p>	<p>1 The conclusions section, I think you had</p> <p>2 previously read in the first sentence of the</p> <p>3 conclusions, the percentage increased risk reported in</p> <p>4 the paper.</p> <p>5 The second sentence says (as read):</p> <p>6 "While the results of case-control</p> <p>7 studies are prone to recall bias,</p> <p>8 especially with intense media</p> <p>9 attention following the</p> <p>10 commencement of litigation in</p> <p>11 2014, the confirmation of an</p> <p>12 association in cohort studies</p> <p>13 between perineal talc use and</p> <p>14 serous invasive ovarian cancer is</p> <p>15 suggestive of a causal</p> <p>16 association."</p> <p>17 Do you see where I was reading?</p> <p>18 A. Yes, I do.</p> <p>19 Q. Okay. So here we see that Penninkilampi is</p> <p>20 acknowledging the recall bias problems of the</p> <p>21 case-control studies; correct?</p> <p>22 A. They are acknowledging that it is a</p> <p>23 possibility.</p> <p>24 Q. Okay.</p> <p>25 A. Okay.</p>

47 (Pages 182 to 185)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 186</p> <p>1 MS. PARFITT: Wait. Are you still --</p> <p>2 thank you.</p> <p>3 Please, finish.</p> <p>4 THE WITNESS: Yes. And, you know, this</p> <p>5 is, again, one of the things that I addressed in my</p> <p>6 report. I very carefully considered recall bias and</p> <p>7 how it could have contributed or not to the elevated</p> <p>8 risk that has been seen across so many studies.</p> <p>9 BY MR. JAMES:</p> <p>10 Q. And one of the -- so within the sentence</p> <p>11 "after acknowledging the recall bias" that we just</p> <p>12 discussed, the Penninkilampi authors emphasize the</p> <p>13 confirmation of an association in cohort studies.</p> <p>14 Do you see that?</p> <p>15 A. I do.</p> <p>16 Q. Okay. Are there cohort studies that support</p> <p>17 the association?</p> <p>18 A. There are three cohort studies that have</p> <p>19 examined talc use and ovarian cancer, and you're</p> <p>20 probably very much aware of them: the Gonzalez study,</p> <p>21 the Houghton -- which was from the Sister Study -- the</p> <p>22 Houghton study, which was the Women's Health</p> <p>23 Initiative; and the Nurses' Health Study, which has</p> <p>24 been published in several of them.</p> <p>25 And as they indicate in here, when you look</p>	<p style="text-align: right;">Page 188</p> <p>1 entirely sure of their rationale for why they looked</p> <p>2 at one rather than the other. There were some</p> <p>3 differences between the studies; like the later study,</p> <p>4 the unexposed group was actually women who had used it</p> <p>5 for less than once a week rather than never used. And</p> <p>6 so they don't really go into the detail why they made</p> <p>7 that decision.</p> <p>8 But investigators will make a judgment</p> <p>9 sometimes about which of a -- which studies to include</p> <p>10 when there's more than one publication from a given</p> <p>11 study.</p> <p>12 Q. And do you know that with respect to the NHS</p> <p>13 cohort, they have published two studies arising from</p> <p>14 the NHS cohort looking at the issue of talc and the</p> <p>15 ovarian cancer association; correct?</p> <p>16 MS. PARFITT: Objection. Form.</p> <p>17 THE WITNESS: They actually -- they</p> <p>18 have published two studies, and data from the Nurses'</p> <p>19 Health Study was also included in at least one other</p> <p>20 publication. I believe Cramer was -- I'm not sure if</p> <p>21 he was the first author or one of the authors where</p> <p>22 they combined data.</p> <p>23 BY MR. JAMES:</p> <p>24 Q. The NHS cohort has published two papers with</p> <p>25 respect to the talc/ovarian cancer association;</p>
<p style="text-align: right;">Page 187</p> <p>1 at the studies that reported on invasive serous -- and</p> <p>2 if you will give me just a second here -- find it on</p> <p>3 this paper. Okay.</p> <p>4 When they report in Table 2 that combining</p> <p>5 the two studies that reported on the histologic</p> <p>6 subtypes, there was a significantly increased risk of</p> <p>7 serous invasive cancer in the cohort studies as well</p> <p>8 in the case-control studies.</p> <p>9 Q. Sorry.</p> <p>10 A. Okay.</p> <p>11 Q. You did pause there.</p> <p>12 A. I did.</p> <p>13 The one study that really found no</p> <p>14 association whatsoever with talc was the Gonzalez</p> <p>15 study, the Sister Study, that has numerous problems</p> <p>16 with it, most specifically in their assessment of the</p> <p>17 talc exposure, the sample size, the duration of</p> <p>18 follow-up.</p> <p>19 Q. And returning to my question about this</p> <p>20 article, were you aware that the Penninkilampi authors</p> <p>21 didn't factor in the Gates 2010 data at all?</p> <p>22 A. When one does a meta-analysis, sometimes when</p> <p>23 data are reported in a couple of reports, you have to</p> <p>24 make a decision about which one to include.</p> <p>25 I believe they used data from the -- I'm not</p>	<p style="text-align: right;">Page 189</p> <p>1 correct?</p> <p>2 A. I just answered the question. It's -- data</p> <p>3 from it was also in another -- in another publication.</p> <p>4 Q. The Gertig 2000 paper reported on the</p> <p>5 talc/ovarian cancer association; correct?</p> <p>6 A. Yes.</p> <p>7 Q. And that's an NHS publication; correct?</p> <p>8 A. It is.</p> <p>9 Q. The Gates 2010 paper reported on talc/ovarian</p> <p>10 cancer association; correct?</p> <p>11 A. That is correct.</p> <p>12 Q. And that's an NHS publication; correct?</p> <p>13 A. Correct.</p> <p>14 Q. An NHS publication of 2010 offered an</p> <p>15 additional ten years of follow-up to the talc/ovarian</p> <p>16 cancer hypothesis; correct?</p> <p>17 MS. PARFITT: Objection. Form.</p> <p>18 THE WITNESS: It was additional</p> <p>19 follow-up, but no update on exposure during that</p> <p>20 time -- period of follow-up.</p> <p>21 BY MR. JAMES:</p> <p>22 Q. For that period of follow-up, they followed</p> <p>23 the study participants for an additional ten years;</p> <p>24 correct?</p> <p>25 MS. PARFITT: Objection. Form.</p>

48 (Pages 186 to 189)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 190	Page 192
<p>1 THE WITNESS: Yes. I answered that 2 already. Yes. 3 BY MR. JAMES: 4 Q. And you agree more follow-up for a cohort is 5 better; correct? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: In general, longer 8 follow-up would be desirable. However, when they're 9 not updating exposure information, that could -- that 10 creates a bias, a possible bias. 11 BY MR. JAMES: 12 Q. Do you think the 2010 data and the Gates 13 paper with respect to the talc ovarian cancer issue is 14 superior to the 2000 data in the Gertig 2000 paper? 15 MS. PARFITT: Objection. Form. 16 THE WITNESS: I already made the point 17 that how they define the unexposed group was different 18 between the two studies; and so including some women 19 who had low levels of exposure in their unexposed 20 group, that could potentially have had the effect of 21 attenuating the association. 22 And so, you know, longer follow-up is 23 generally better, but some of the other things they 24 did, that's -- they were not so good. 25</p>	<p>1 Q. So one of your complaints -- 2 A. So I -- 3 Q. Sorry. 4 A. Okay. 5 Q. One of your issues with the cohort studies is 6 lack of follow-up; correct? 7 A. For -- yes, for -- there are -- it's one of 8 several concerns I have about the cohort studies. 9 Q. And the Penninkilampi study did not factor in 10 the additional period of follow-up through the 2010 11 paper; correct? 12 A. I don't believe they did. I think they went 13 with the earlier study. 14 Q. In fact, they didn't even cite to the Gates 15 2010 data, did they? 16 MS. PARFITT: Objection. 17 THE WITNESS: No, they -- they didn't. 18 BY MR. JAMES: 19 Q. And they didn't offer any explanation about 20 why they went with the earlier study, did they? 21 A. Not that I recall. 22 Q. And do you understand that in the 2010 NHS 23 paper through Gates, the association with serous 24 ovarian cancer washed out? 25 MS. PARFITT: Objection to form.</p>
Page 191	Page 193
<p>1 BY MR. JAMES: 2 Q. Elsewhere in your report, you do complain 3 about lack of follow-up in the cohort studies, don't 4 you? 5 A. I do mention that as one of the limitations, 6 yes. 7 Q. And you specifically discuss the NHS cohort 8 as having a period of -- I believe you say it's 9 14 years; is that right? 10 A. From -- yeah. I -- I can't remember 11 specifically. It's from the 1980s to -- I don't 12 remember the exact date of the last -- the last date 13 of follow-up in their papers. 14 Q. And, again, that's the exposure period that 15 Penninkilampi is looking at as well; correct? 16 Or excuse me, not the exposure period, the 17 period of time that they follow the study 18 participants; correct? 19 Penninkilampi is looking at from 20 questionnaire to 2000; correct? 21 A. Correct. 22 Q. Okay. And when you say in your report that 23 the NHS study has a 14-year follow-up period, that's 24 what you're looking at too, as well; correct? 25 A. Right. From the time of exposures --</p>	<p>1 THE WITNESS: "Washed out," I don't 2 like that term. But again, I fully acknowledge that 3 the later study showed weaker associations, yes. 4 BY MR. JAMES: 5 Q. And the association for serous invasive 6 ovarian cancer in the Gates 2010 paper was not 7 statistically significant; correct? 8 A. I believe that is correct. 9 Q. So when you include the critique in your 10 report about the follow-up being a 14-year period, you 11 also, like Penninkilampi, aren't crediting the 12 additional ten years of follow-up that the Gates paper 13 published on; correct? 14 MS. PARFITT: Objection to form. 15 THE WITNESS: "Aren't crediting the 16 additional ten years of follow-up." 17 You know, as I have stated before, when 18 people do meta-analyses, they will make decisions 19 about which studies to include. I acknowledge that 20 Penninkilampi didn't describe in detail why they went 21 with the Gertig rather than a later study. 22 My understanding, however, is that other 23 people -- other meta-analyses have looked at -- have 24 included the later study, and the overall conclusions 25 were not changed in any real way.</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 194	Page 196
<p>1 BY MR. JAMES: 2 Q. Well, Penninkilampi, you say, didn't describe 3 in detail about why they went with the earlier study, 4 but, in truth, they didn't describe it at all. 5 MS. PARFITT: Objection. 6 THE WITNESS: That's -- that's correct. 7 BY MR. JAMES: 8 Q. And when you refer to other studies that 9 have, in fact, looked at the Gates 2010 cohort data 10 that provides a longer period of follow-up, those 11 papers have necessarily noted that the serous 12 relationship found in Gertig 2000 disappeared in 2010; 13 correct? 14 MS. PARFITT: Objection. Form. 15 THE WITNESS: Can you -- can we -- tell 16 me which -- specifically which article you're -- 17 BY MR. JAMES: 18 Q. Sure. Let's turn to the Berge article. 19 A. Okay. 20 Q. The Berge article was marked as 21 Exhibit No. 21. And you have it before you, Doctor? 22 A. I do. 23 Q. Okay. And if you turn to Figure 2, which is 24 on page 254, do you see that there that in the forest 25 plot, they have listed the cohort studies at the</p>	<p>1 BY MR. JAMES: 2 Q. They're heterogeneous. Did I pronounce that 3 correctly? 4 A. No. Heterogeneous. 5 Q. Heterogeneous. Thank you. I figured I got 6 that wrong. 7 So what they're saying there is that the 8 results by the study design are different; right? 9 A. That's -- yes, that's what they are saying. 10 Q. And here we see, again, that this study used 11 the more recent data; correct? 12 MS. PARFITT: Objection. Form. 13 THE WITNESS: It used the more recent 14 publication from the Nurses' Health Study, yes. 15 BY MR. JAMES: 16 Q. Which includes the more recent data; correct? 17 MS. PARFITT: Objection. 18 THE WITNESS: Yes. 19 BY MR. JAMES: 20 Q. On page 8 of your report, Dr. Moorman, you 21 say at the bottom paragraph (as read): 22 "Cohort studies and case-control 23 studies each have advantages and 24 disadvantages for assessing talc 25 as a risk factor for ovarian</p>
Page 195	Page 197
<p>1 bottom; correct? 2 A. Correct. 3 Q. Okay. And there they report data from the 4 Gates 2010 study; correct? 5 A. Correct. 6 Q. Okay. They do not report the data from the 7 Gertig 2000 paper; correct? 8 A. That is correct. 9 Q. And if you look at the conclusions of the 10 Berge authors -- and we talked about this before -- 11 but if you look at the abstract of the paper, 12 Dr. Moorman, the authors say (as read): 13 "The heterogeneity of results by 14 study design, however, detracts 15 from a causal interpretation of 16 this association." 17 Do you see that? 18 A. Yes. You've asked that before. Yes. 19 Q. And what the authors there are saying is that 20 the results from the case-control studies, the 21 meta-analyses of the case-control studies, and the 22 results of the meta-analyses of the cohort studies are 23 different; right? 24 MS. PARFITT: Objection. 25 THE WITNESS: They -- yes.</p>	<p>1 cancer, and one study design is 2 not clearly superior to the 3 other." 4 Do you see where I was reading that? 5 A. Yes, I do. 6 Q. So your expert opinion in this case is that 7 the cohort studies on talc ovarian cancer and the 8 case-control studies on talc ovarian cancer are on 9 equal footing? 10 A. I think -- again, using terminology like 11 "equal footing," it's -- I wouldn't really describe it 12 like that. 13 I think that case-control studies and cohort 14 studies are both well-established, well-accepted 15 methods for studying cancer epidemiology. There are 16 strengths and weaknesses to each design, as I have 17 indicated here. And some of them very -- some of the 18 strengths and weaknesses are very specific to this 19 exposure and outcome. 20 Q. Doesn't the body of talc ovarian cancer 21 literature that you've looked at for your MDL opinions 22 emphasize the importance of cohort data on the issue? 23 MS. PARFITT: Objection. Form. 24 THE WITNESS: I considered all of the 25 epidemiologic data; and when we look at the body of</p>

50 (Pages 194 to 197)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 198</p> <p>1 literature, more of the literature comes from 2 case-control studies than from cohort studies. So all 3 of the data are important. There just happen to be 4 more case-control studies than cohort studies. 5 BY MR. JAMES: 6 Q. But your testimony is that the cohorts are 7 not superior to the case-controls, and the 8 case-controls are not superior to the cohorts; 9 correct? 10 A. As I describe in my report -- the same page, 11 I say (as read): 12 "Rather than making a judgment 13 based only on the overall study 14 design, the evaluation and 15 interpretation of the findings of 16 the studies must consider the 17 strengths and weaknesses of the 18 individual studies." 19 And I think that I did consider that. 20 I considered strengths and weaknesses of the cohort 21 studies. I considered strengths and weaknesses of the 22 case-control studies. 23 Q. And you're not claiming that the study design 24 of these studies -- the cohort versus the 25 case-control -- one is superior to the other? You're</p>	<p style="text-align: right;">Page 200</p> <p>1 And it's the number of cases rather than the overall 2 size of the cohort that contributes to the statistical 3 power. And that doesn't address all the other 4 problems with that study. 5 But sometimes people will mistakenly say 6 these large studies -- you know, this large study, 7 40,000 people, and they didn't find an association. 8 But they're not looking into all the limitations of 9 that particular study. 10 BY MR. JAMES: 11 Q. Okay, Dr. Moorman, I'm going to object to the 12 nonresponsive nature of your answer. 13 A. I -- I think that I was responsive, but 14 please ask your question again. 15 Q. Okay. So the question that I asked you is 16 whether you are aware that the body of literature that 17 you've looked at has generally emphasized the 18 importance of cohort data on this topic. The answer 19 is yes or the answer is no. 20 MS. PARFITT: The answer is -- first, 21 I object to the question. And the witness has 22 answered the question several times. Your time. 23 You're on your clock. 24 BY MR. JAMES: 25 Q. Are you aware that the body of literature has</p>
<p style="text-align: right;">Page 199</p> <p>1 not claiming that? 2 MS. PARFITT: Objection. Asked and 3 answered several times. 4 THE WITNESS: Right. I -- again, 5 I think that I have answered that, that they -- the 6 study designs are both well-accepted study designs; 7 they have advantages and disadvantages; and so you 8 have to look at some of the specific characteristics 9 of the individual studies. 10 BY MR. JAMES: 11 Q. And so the body of talc literature that 12 you've looked at, whether it be cohort studies, 13 meta-analyses, case-control studies, are you aware 14 that that body of literature has generally emphasized 15 the importance of cohort data on this topic? 16 MS. PARFITT: Objection. Misstates the 17 record -- scientific record. 18 THE WITNESS: I am aware -- I have read 19 some studies that mistakenly say that the cohort 20 studies, because they involve 40,000 or 60,000 people, 21 that they provide more of the evidence than all the 22 case-control studies, which are generally smaller. 23 However, just, again, to take the example of 24 the Gonzalez sisters study, that's a cohort with 25 40,000 people in it, but there were only 154 cases.</p>	<p style="text-align: right;">Page 201</p> <p>1 emphasized the importance of cohort data? Are you 2 aware of that? Yes or no? 3 MS. PARFITT: Objection. 4 THE WITNESS: I -- I disagree that -- 5 your characterization of it. 6 BY MR. JAMES: 7 Q. Then, the answer is no. 8 A. No. You asked am I aware -- 9 Q. The answer is yes or it's no, Dr. Moorman. 10 I have limited time to ask questions today. 11 Were you aware -- are you aware that the 12 body of literature on talc and ovarian cancer has 13 emphasized the importance of cohort data on this 14 topic? 15 MS. PARFITT: Objection. Form. 16 THE WITNESS: I don't think -- 17 MS. PARFITT: Asked and answered. 18 THE WITNESS: -- the statement is true. 19 I think that the -- 20 BY MR. JAMES: 21 Q. So then the answer is no. 22 MS. PARFITT: Stop. Let her answer. 23 THE WITNESS: No. You're asking me if 24 I'm aware -- 25 MS. PARFITT: Why do you ask her the</p>

51 (Pages 198 to 201)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 202	Page 204
<p>1 same question?</p> <p>2 THE WITNESS: -- that this has</p> <p>3 emphasized that. And I don't think that is it at all.</p> <p>4 I think that the body of literature</p> <p>5 emphasizes again and again and again that of the</p> <p>6 roughly 25 to 30 studies, only three of them are</p> <p>7 cohort studies.</p> <p>8 It's part of the data on the topic, but it's</p> <p>9 just part of it. So to say that it has emphasized the</p> <p>10 importance of cohort data, I don't agree with that</p> <p>11 statement.</p> <p>12 BY MR. JAMES:</p> <p>13 Q. I marked the Houghton WHI study as</p> <p>14 Exhibit No. 25, and I'm going to hand you two copies.</p> <p>15 (Exhibit No. 25 was marked for identification.)</p> <p>16 THE WITNESS: Thank you.</p> <p>17 BY MR. JAMES:</p> <p>18 Q. All right. Dr. Moorman, you see here in the</p> <p>19 abstract, the "Background" section of the paper, the</p> <p>20 authors of the WHI study in 2014 say that (as read):</p> <p>21 "The purpose of this analysis was</p> <p>22 to assess perineal powder use and</p> <p>23 risk of ovarian cancer</p> <p>24 prospectively."</p> <p>25 Correct?</p>	<p>1 exposure."</p> <p>2 Do you see where I read that?</p> <p>3 A. I do.</p> <p>4 Q. Okay. Again, do you agree with that</p> <p>5 statement as a general proposition?</p> <p>6 A. I would like to point out there are --</p> <p>7 potential reason, a potential for an overestimation.</p> <p>8 And in my own report, I acknowledge the potential for</p> <p>9 recall bias, and I go back to explain why I don't</p> <p>10 think that recall bias is a full explanation for this</p> <p>11 association.</p> <p>12 Q. Nevertheless, you will agree with me that the</p> <p>13 authors of this paper are acknowledging the importance</p> <p>14 of cohort data? Agree?</p> <p>15 MS. PARFITT: Objection.</p> <p>16 THE WITNESS: As you would expect the</p> <p>17 investigators on a cohort study to do.</p> <p>18 BY MR. JAMES:</p> <p>19 Q. And the answer was yes --</p> <p>20 A. Yes.</p> <p>21 Q. -- comma, as you would expect?</p> <p>22 MS. PARFITT: Objection.</p> <p>23 THE WITNESS: Yes.</p> <p>24 MR. JAMES: I'm going to mark as the</p> <p>25 next exhibit the Gertig 2000 paper, which is</p>
Page 203	Page 205
<p>1 A. That is what it says, yes.</p> <p>2 Q. Okay. And if we look towards page 5, we see,</p> <p>3 at the top of the left-hand column, the authors there</p> <p>4 emphasize (as read):</p> <p>5 "The prospective nature of our</p> <p>6 study would eliminate the</p> <p>7 potential for recall bias."</p> <p>8 Do you see that?</p> <p>9 A. I do see that.</p> <p>10 Q. Do you agree with that general proposition?</p> <p>11 "Yes" or "no"?</p> <p>12 A. It eliminates the potential for recall bias.</p> <p>13 It does not eliminate the potential for inaccurate</p> <p>14 recall.</p> <p>15 Q. And if you look at page 4, it's the preceding</p> <p>16 set of sentences, the authors note -- quote -- at the</p> <p>17 bottom of the right column (as read):</p> <p>18 "One potential reason that</p> <p>19 case-control studies have found</p> <p>20 slight increases in risk is the</p> <p>21 potential for an overestimation of</p> <p>22 the true association due to recall</p> <p>23 bias, because the participants are</p> <p>24 aware of their ovarian cancer</p> <p>25 status when reporting powder</p>	<p>1 Exhibit No. 26.</p> <p>2 (Exhibit No. 26 was marked for identification.)</p> <p>3 BY MR. JAMES:</p> <p>4 Q. Again, this is the NHS 2000 paper; correct?</p> <p>5 A. That is correct.</p> <p>6 Q. And we see that in the abstract of this</p> <p>7 cohort paper, the authors state at the -- well, it's</p> <p>8 not in the abstract -- it's right above the "Methods"</p> <p>9 section, the authors state (as read):</p> <p>10 "Despite the relative consistency</p> <p>11 among studies, the limited</p> <p>12 supporting biologic evidence,</p> <p>13 together with the possibility of</p> <p>14 recall and selection bias in</p> <p>15 case-control studies, has raised</p> <p>16 questions about the plausibility</p> <p>17 of the association. We,</p> <p>18 therefore, prospectively examined</p> <p>19 the relationship between perineal</p> <p>20 talc use and ovarian cancer risk</p> <p>21 in a large cohort of US women."</p> <p>22 Do you see where I read that?</p> <p>23 A. Yes, I do.</p> <p>24 Q. And again, methodologically, the authors of</p> <p>25 this cohort paper are emphasizing the importance of</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 206</p> <p>1 cohort data on the topic; correct?</p> <p>2 MS. PARFITT: Objection.</p> <p>3 THE WITNESS: Yes. Again, they</p> <p>4 emphasize the importance of doing it prospectively, as</p> <p>5 you would expect the investigators on a cohort study</p> <p>6 to do.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. Do you think that's just because there's some</p> <p>9 sort of subjective bias the authors of that cohort</p> <p>10 paper have towards cohorts? Do you think that's just</p> <p>11 their personal opinion?</p> <p>12 MS. PARFITT: Objection.</p> <p>13 THE WITNESS: I have no way of knowing</p> <p>14 what their opinion is.</p> <p>15 BY MR. JAMES:</p> <p>16 Q. A number of the meta-analyses that we've</p> <p>17 looked at today and that you looked at to inform your</p> <p>18 report have also talked about the benefits of cohort</p> <p>19 data. And I've asked that question before, and that's</p> <p>20 where we -- that's where we sort of ran into issues,</p> <p>21 so I'll just strike that question.</p> <p>22 If you can turn to -- back to the</p> <p>23 Penninkilampi study. And the Penninkilampi study is</p> <p>24 the recent meta-analysis that you cited 14 times in</p> <p>25 your report; correct?</p>	<p style="text-align: right;">Page 208</p> <p>1 again stressing the desire for cohort data on this</p> <p>2 topic; correct?</p> <p>3 MS. PARFITT: Objection. Misstates the</p> <p>4 evidence.</p> <p>5 THE WITNESS: When -- if we were to</p> <p>6 look at a cohort study where women were enrolled in</p> <p>7 the study early in their life when they started using</p> <p>8 talc and they were followed throughout their life and</p> <p>9 exposure information was updated throughout the period</p> <p>10 of follow-up and you followed them for 50 years, that</p> <p>11 would be a wonderful way -- a stronger design than to</p> <p>12 do a case-control study. So I could not disagree with</p> <p>13 that.</p> <p>14 But we're being asked to make a judgment on</p> <p>15 the data that we have here -- here and now, not</p> <p>16 something that's decades away.</p> <p>17 BY MR. JAMES:</p> <p>18 Q. Do you agree that case-control studies are</p> <p>19 low-level evidence?</p> <p>20 A. No, I do not agree with that.</p> <p>21 Q. Do you know that the Penninkilampi authors</p> <p>22 referred to case-control studies as low-level</p> <p>23 evidence?</p> <p>24 A. I see that in their paper.</p> <p>25 Q. Do you --</p>
<p style="text-align: right;">Page 207</p> <p>1 MS. PARFITT: Objection. Form.</p> <p>2 THE WITNESS: As stated below -- or</p> <p>3 stated above, I have cited it. I don't know how many</p> <p>4 times.</p> <p>5 BY MR. JAMES:</p> <p>6 Q. And meta-analyses also are what you refer to</p> <p>7 in your report as some of the strongest evidence;</p> <p>8 correct?</p> <p>9 A. Yes, that is correct.</p> <p>10 Q. Okay. And so the authors of this</p> <p>11 meta-analysis, on page 47 in the conclusion section,</p> <p>12 which we have looked at already, again note that</p> <p>13 case-control studies are "prone to recall bias";</p> <p>14 right?</p> <p>15 A. That's what it says, yes.</p> <p>16 Q. Okay. And then if you continue on past the</p> <p>17 section that we've already read -- and actually, it</p> <p>18 begins at the bottom of page 47 and carries to 48 --</p> <p>19 but the authors state (as read):</p> <p>20 "Additional epidemiologic evidence</p> <p>21 from prospective studies with</p> <p>22 attention to effects within</p> <p>23 ovarian cancer subtype is</p> <p>24 warranted."</p> <p>25 So here the authors of Penninkilampi are</p>	<p style="text-align: right;">Page 209</p> <p>1 A. I --</p> <p>2 Q. I'm sorry.</p> <p>3 A. I will disagree with that. It's -- just</p> <p>4 using the example of my own study, the AACES study.</p> <p>5 Of all the studies that have looked at talc and</p> <p>6 ovarian cancer, I believe that one is the one that has</p> <p>7 been most recently funded. So about 2009, 2010. It's</p> <p>8 quite an expensive study, and I can't imagine that the</p> <p>9 National Cancer Institute would have invested that</p> <p>10 much money in the study if they thought that we were</p> <p>11 only going to get low-level evidence.</p> <p>12 MS. PARFITT: Scott, we've been going</p> <p>13 about an hour and ten.</p> <p>14 You may want to keep going? Just let me</p> <p>15 know.</p> <p>16 THE WITNESS: I could use a break.</p> <p>17 MR. JAMES: May I finish this line? Is</p> <p>18 that okay with you?</p> <p>19 THE WITNESS: Yes.</p> <p>20 MR. JAMES: Everyone?</p> <p>21 MS. PARFITT: Sure.</p> <p>22 BY MR. JAMES:</p> <p>23 Q. Dr. Moorman, if you can turn with me to the</p> <p>24 Langseth study. It's Exhibit 22. And this will be</p> <p>25 the last series of questions, and then we'll take our</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 210	Page 212
<p>1 break.</p> <p>2 A. Langseth -- okay. The exhibit number is</p> <p>3 incorrect.</p> <p>4 Q. Oh, you're right. And I'm going to fix that</p> <p>5 at break. Thank you.</p> <p>6 A. Okay.</p> <p>7 Q. If you turn with me to page -- well, you</p> <p>8 don't have to turn. It's page 358. It's the first</p> <p>9 page of the article. And, again, Langseth is one of</p> <p>10 the meta-analyses upon which you rely; correct?</p> <p>11 A. Correct.</p> <p>12 Q. And the meta-analyses authors here say, in</p> <p>13 the left-hand column at the bottom, the second</p> <p>14 sentence of the bottom paragraph, they say (as read):</p> <p>15 "In the cohort study, arguably the</p> <p>16 strongest study because of its</p> <p>17 partly prospective ascertainment</p> <p>18 of exposure, there was no</p> <p>19 association between cosmetic talc</p> <p>20 use and risk of all subtypes of</p> <p>21 ovarian cancer combined."</p> <p>22 Do you see that?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. You agree with the Langseth authors</p> <p>25 that the cohort study is arguably the strongest study</p>	<p>1 Q. And you cite Narod for your comments about</p> <p>2 power in the cohorts; correct?</p> <p>3 A. Yes.</p> <p>4 Q. Have you analyzed the calculations performed</p> <p>5 by Narod? Have you separately analyzed his</p> <p>6 calculations?</p> <p>7 A. No, I did not.</p> <p>8 Q. Have you considered any other commentaries or</p> <p>9 articles looking at the issue of power in the cohort</p> <p>10 studies in the talc ovarian cancer literature?</p> <p>11 A. I -- I'm trying to remember specifically. It</p> <p>12 seems like the Sister Study might have mentioned power</p> <p>13 as a limitation of their study because of the number</p> <p>14 of cases.</p> <p>15 Q. Did you consider -- let me just hand this to</p> <p>16 you. We already have it marked. It's the Berge</p> <p>17 article, which is Exhibit 21.</p> <p>18 A. Okay.</p> <p>19 Q. And I'm turning to page 253. And at the</p> <p>20 far -- the right column, top paragraph, and halfway</p> <p>21 down through that paragraph, the authors state</p> <p>22 (as read):</p> <p>23 "It should be noted that the</p> <p>24 cohort studies included in the</p> <p>25 meta-analyses comprised a total of</p>
Page 211	Page 213
<p>1 because of its prospective nature?</p> <p>2 A. I really can't say that I agree with that,</p> <p>3 because the prospective aspect of it is certainly a</p> <p>4 positive for the study, but the way they did exposure</p> <p>5 assessment kind of weakened the study.</p> <p>6 So I think that there were some very well</p> <p>7 done case-control studies, so I wouldn't necessarily</p> <p>8 say this was the strongest study.</p> <p>9 MR. JAMES: And now is a good time for</p> <p>10 the break.</p> <p>11 THE WITNESS: Okay.</p> <p>12 MR. JAMES: Thank you.</p> <p>13 THE VIDEOGRAPHER: Going off record at</p> <p>14 3:02 p.m.</p> <p>15 (Recess taken from 3:02 p.m. to 3:16 p.m.)</p> <p>16 THE VIDEOGRAPHER: Back on record at</p> <p>17 3:16 p.m.</p> <p>18 BY MR. JAMES:</p> <p>19 Q. Dr. Moorman, on page 25 of your report, you</p> <p>20 make a comment about power and the cohort studies;</p> <p>21 correct?</p> <p>22 A. Can you --</p> <p>23 Q. It's the bottom of first paragraph, where you</p> <p>24 cite the Narod article.</p> <p>25 A. Yes.</p>	<p>1 429 cases of ovarian cancer</p> <p>2 exposed to genital talc and 943</p> <p>3 unexposed cases. The statistical</p> <p>4 power of the meta-analysis of</p> <p>5 these cohort studies to detect a</p> <p>6 relative risk of 1.25, similar to</p> <p>7 the result of meta-analyses of</p> <p>8 case-control studies, was .99.</p> <p>9 Thus low power of cohort studies</p> <p>10 cannot be invoked as an</p> <p>11 explanation of the heterogeneity</p> <p>12 of results."</p> <p>13 You see where I was reading?</p> <p>14 A. I do.</p> <p>15 Q. Have you considered this portion of the Berge</p> <p>16 article before?</p> <p>17 A. I have looked at this article, and I have</p> <p>18 considered all aspects of it, as I did all of the</p> <p>19 other meta-analyses and articles.</p> <p>20 Q. You did not cite the Berge article with</p> <p>21 regard to the issue of power in your report; correct?</p> <p>22 MS. PARFITT: Objection. Form.</p> <p>23 THE WITNESS: No, I -- I did not.</p> <p>24 BY MR. JAMES:</p> <p>25 Q. Okay. And why is that?</p>

54 (Pages 210 to 213)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 214	Page 216
<p>1 A. I can't cite any specific reason.</p> <p>2 Q. Is that because this conflicts with your</p> <p>3 litigation opinion on power?</p> <p>4 MS. PARFITT: Objection. Form.</p> <p>5 THE WITNESS: No. I -- I don't -- that</p> <p>6 was not my reason, no.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. Do you have any reason to disagree with the</p> <p>9 power analysis set forth in the Berge paper?</p> <p>10 A. I -- I don't have a reason to disagree with</p> <p>11 the power issue, but I think that it's only one part</p> <p>12 of the picture, that there are other factors that</p> <p>13 could contribute to differences in the findings</p> <p>14 between the cohort studies and the case-control</p> <p>15 studies.</p> <p>16 Q. With respect to this precise power</p> <p>17 calculation in the Berge paper, do you have any</p> <p>18 criticisms of this power calculation?</p> <p>19 A. They do not provide much detail on how they</p> <p>20 calculated it, so there's really -- I can't say if</p> <p>21 they did it correctly or not. But I -- I just can't</p> <p>22 comment on it. It's just a single sentence there.</p> <p>23 Q. Similar to the Narod sentence that you</p> <p>24 reviewed?</p> <p>25 A. I --</p>	<p>1 but with respect to the issue of follow-up -- it's the</p> <p>2 paragraph above the Narod comment.</p> <p>3 Do you see where I am?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. And there, we talk about -- excuse me.</p> <p>6 There, you talk about the follow-up for the cohort</p> <p>7 studies; correct?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. And with respect to the NHS follow-up,</p> <p>10 there is where you report 14 years of follow-up;</p> <p>11 right?</p> <p>12 A. Correct.</p> <p>13 Q. And as we discussed earlier today, that does</p> <p>14 not account for the additional ten years of data as</p> <p>15 reflected by the Gates 2010 paper; correct?</p> <p>16 A. What I am referring here, I'm describing the</p> <p>17 three cohort studies in the most recent meta-analyses</p> <p>18 and what they reported in that meta-analysis --</p> <p>19 Q. Understood.</p> <p>20 A. Okay.</p> <p>21 Q. So you're referring there to the</p> <p>22 Penninkilampi meta-analysis; correct?</p> <p>23 A. I believe that is the case. Let me check the</p> <p>24 reference. Yes.</p> <p>25 Q. So Penninkilampi reports the 14 years of</p>
Page 215	Page 217
<p>1 Q. Let me rephrase it if it helps.</p> <p>2 Did you separately assess the Berge --</p> <p>3 excuse me -- the power calculation in either the Narod</p> <p>4 article or the Berge article?</p> <p>5 A. If I may go back to my report for just a</p> <p>6 moment.</p> <p>7 Q. Sure.</p> <p>8 A. I think that this statement that I have</p> <p>9 here -- I'm -- I think my intent in my report was</p> <p>10 indicating that the lack of statistical significance</p> <p>11 in the individual studies was a power concern.</p> <p>12 Berge was talking about the statistical</p> <p>13 power for the combined studies. So I think that there</p> <p>14 is some distinction there between what I'm referring</p> <p>15 to individual studies versus what Berge is describing</p> <p>16 as the power of the combined analysis.</p> <p>17 Q. Well, Berge is saying that the low power of</p> <p>18 cohort studies cannot be invoked as an explanation for</p> <p>19 the heterogeneity of results.</p> <p>20 Do you agree or disagree with that</p> <p>21 statement?</p> <p>22 A. When they are combining them, I -- I don't</p> <p>23 disagree with that. I think there are other reasons</p> <p>24 that can explain the heterogeneity.</p> <p>25 Q. On page 25, we've touched upon this already,</p>	<p>1 follow-up; correct?</p> <p>2 A. I believe so.</p> <p>3 Q. And we know that the Penninkilampi paper did</p> <p>4 not include the additional 10 years of follow-up as</p> <p>5 reflected by the Gates 2010 paper; correct?</p> <p>6 A. Yes. We have already -- you've already asked</p> <p>7 and I've already answered that.</p> <p>8 Q. And then the next one you discuss is the WHI</p> <p>9 study where you are reporting Penninkilampi's</p> <p>10 reporting of 12.4 years of follow-up; correct?</p> <p>11 A. That is correct.</p> <p>12 Q. And do you know that the follow-up period in</p> <p>13 the WHI -- do you know that the WHI asked about</p> <p>14 duration of talc use?</p> <p>15 A. May I go back to that study?</p> <p>16 Q. Sure.</p> <p>17 A. Do you --</p> <p>18 Q. It's 25.</p> <p>19 A. Yes, they describe in their exposure</p> <p>20 assessment, that they did ask about duration of use</p> <p>21 using five categories from less than a year all the</p> <p>22 way up to 20 or more years.</p> <p>23 Q. And so we know that they -- they followed the</p> <p>24 study participants for, according to Penninkilampi,</p> <p>25 12.4 years. But, in addition to that, they also asked</p>

55 (Pages 214 to 217)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 218	Page 220
<p>1 about the -- study participants about their prior 2 duration of usage; correct? 3 A. They asked about that, but I think that one 4 has to consider some of the caveats that go along with 5 that. These -- may I continue? 6 These women, they report that they were, on 7 average, 63 years of age when they -- at baseline, so 8 at the start of enrollment in the cohort. So they 9 were asking them to recall an exposure that went back, 10 for many women, that probably started in their teens 11 or twenties. So there was certainly the possibilities 12 of some inaccurate recall because they were asking 13 them to recall an exposure that went back quite a few 14 years. 15 Another consideration with this study is 16 they excluded roughly -- let's see -- the cohort 17 was -- they started off with 90-some-thousand women in 18 the cohort, and they excluded any history of any women 19 with cancer at baseline, which is appropriate to do, 20 but the potential concern about that is, if there were 21 talc users who had developed ovarian -- or had 22 developed ovarian cancer before the follow-up began, 23 that would never be captured. 24 MR. JAMES: Okay. Dr. Moorman, just 25 very respectfully, I'm going to have to object to the</p>	<p>1 excuse me -- page 26, you discuss updating exposure 2 information in the cohort studies. 3 A. Yes. 4 Q. Do you have any basis to dispute the accuracy 5 of the reported talc use at the time it was initially 6 ascertained in the cohort studies? 7 A. The accuracy of the reported talc use at the 8 time that they started follow-up in the cohorts. 9 Q. Correct. 10 A. I believe that, when you are asking people to 11 recall exposures that occurred over a long period of 12 time, there will be some inadvertent inaccuracies. 13 Q. And are you saying with respect to questions 14 about duration? 15 A. It could be with ever use or with duration. 16 Some women who used it might have forgotten and never 17 reported it. So that's just kind of an inherent 18 problem anytime you ask someone to recall exposures, 19 particularly if they might have occurred decades ago. 20 Q. Is that true for the case-control studies as 21 well? 22 A. Yes. In my report, I indicate that -- I make 23 the distinction between recall bias and inaccurate 24 recall and indicate that inaccurate recall -- 25 specifically on page 21, make the distinction between</p>
Page 219	Page 221
<p>1 nonresponsive portion of the answer. 2 BY MR. JAMES: 3 Q. So the question that I asked is not the 4 question that you ended up answering. 5 A. I did answer your question, I believe. 6 Q. Okay. I didn't ask you for your critiques of 7 the WHI. I asked you about the follow-up issue. 8 Okay? Do we need to look at the question again? 9 I asked -- my question is: 10 "Question: But in addition to that, 11 they also asked about -- the study 12 participants about their prior 13 duration of usage; correct?" 14 A. And I answered it but thought that there were 15 important relevant considerations. 16 MR. JAMES: Can we go off the record 17 for a second -- 18 MS. PARFITT: Yes. 19 MR. JAMES: -- please? 20 THE VIDEOGRAPHER: Off record at 3:29. 21 (Discussion off the record.) 22 THE VIDEOGRAPHER: Back on record at 23 3:31 p.m. 24 BY MR. JAMES: 25 Q. On page 25 of your report, Dr. Moorman --</p>	<p>1 recall bias and inaccurate recall that is difficult -- 2 inaccurate recall and exposure that is difficult to 3 remember with precision. 4 And that's an issue with any type of study 5 when you're asking people to recall past exposures. 6 Q. And transitioning to the topic that you 7 brought up, which is the recall bias. We can stay on 8 page 216 your report. 9 A. Yes. 10 Q. And there, you address -- at the bottom 11 paragraph, you say that (as read): 12 "Recall bias, which theoretically 13 could result in the bias estimate 14 of the relative risk, must be 15 considered." 16 Do you see where I am? 17 A. I do. 18 Q. And you cite three situations where recall 19 bias would be a "particular threat" to a study's 20 validity; right? 21 A. Yes. 22 Q. And with -- let's walk through those three 23 together. 24 The first is -- the first threat that you 25 identify is "if the exposure of interest is one that</p>

56 (Pages 218 to 221)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 222	Page 224
<p>1 could be considered sensitive"; right?</p> <p>2 A. Yes.</p> <p>3 Q. Okay. And then you address that reason in</p> <p>4 turn on the next page, on page 22 of your report?</p> <p>5 A. Yes.</p> <p>6 Q. And you state there that (as read):</p> <p>7 "In regard to the situation,</p> <p>8 genital talc use would 'not be</p> <p>9 considered a particularly</p> <p>10 sensitive topic."</p> <p>11 Right?</p> <p>12 A. That's what I state in my report, yes.</p> <p>13 Q. Okay. And what basis do you have for that</p> <p>14 statement? Do you cite to anything? Have you</p> <p>15 conducted any studies to support that statement? What</p> <p>16 scientific basis do you have for that statement?</p> <p>17 A. This is based on my professional judgment,</p> <p>18 based on years and years of doing studies where we</p> <p>19 collect data, getting feedback from interviewers. In</p> <p>20 our studies, we ask about a lot of personal things,</p> <p>21 you know, their menstrual history, their contraceptive</p> <p>22 history, those kind of things.</p> <p>23 And I have never gotten the impression that</p> <p>24 these were things that women considered sensitive and</p> <p>25 did not want to reveal, whereas when you get into</p>	<p>1 them, or any reason why a woman, if she's telling you</p> <p>2 her whole pregnancy and menstrual history, why she</p> <p>3 would feel embarrassed about her use of genital talc.</p> <p>4 Q. And do you have any empirical data to support</p> <p>5 that opinion?</p> <p>6 A. I am unaware of any empirical data that</p> <p>7 specifically addresses that.</p> <p>8 Q. Okay. The second situation you identify on</p> <p>9 page 21 and then discuss on page 22 is if -- is if the</p> <p>10 study hypotheses are known to the study subjects or</p> <p>11 interviewers.</p> <p>12 Do you see that?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. And your analysis is on page 22.</p> <p>15 What did you do to evaluate this factor?</p> <p>16 A. Whether the study hypotheses are known to the</p> <p>17 study subjects or interviewers?</p> <p>18 Q. Correct. With respect to the talc ovarian</p> <p>19 cancer literature.</p> <p>20 A. Okay. Again, this is based on my experience</p> <p>21 in having done epidemiologic studies for many years.</p> <p>22 As I state here, it's standard practice in</p> <p>23 epidemiologic research where we're not discussing the</p> <p>24 hypotheses with the interviewers. We're asking a lot</p> <p>25 of questions. Some thought to increase risk; some</p>
Page 223	Page 225
<p>1 other topics, say -- like, I give the example of</p> <p>2 induced abortion, that, I have heard from some of our</p> <p>3 interviewers, that sometimes that evokes strong</p> <p>4 emotions in the women.</p> <p>5 And so I think that, you know, there are</p> <p>6 some exposures that are sensitive, as I describe, that</p> <p>7 women might be hesitant to report. And I contrast</p> <p>8 that with things that are personal but not</p> <p>9 particularly sensitive.</p> <p>10 When a woman has agreed to be in a study,</p> <p>11 she knows that we're going to be asking some of these</p> <p>12 questions. And I have never heard any comments from</p> <p>13 any of the interviewers in the many studies I've done</p> <p>14 that this was a question that women felt uncomfortable</p> <p>15 with.</p> <p>16 Q. Do you acknowledge the possibility that a</p> <p>17 person's use of a cosmetic talcum powder in their</p> <p>18 genital region could be viewed by some as a sensitive</p> <p>19 topic?</p> <p>20 A. I -- again, I -- I kind of make the</p> <p>21 distinction between something that is personal -- and</p> <p>22 we ask them a lot of personal questions, but it's --</p> <p>23 I don't see any aspect of that that would seem</p> <p>24 particularly sensitive, why someone might be</p> <p>25 embarrassed or feel that someone was going to judge</p>	<p>1 thought to decrease risk. It's standard that you</p> <p>2 would not really discuss the hypotheses with the</p> <p>3 interviewers.</p> <p>4 And, similarly, when we invite or ask women</p> <p>5 to be in our studies, we will tell them that, you</p> <p>6 know, it is a study of ovarian cancer, but we're not</p> <p>7 telling them which factors we think might be</p> <p>8 associated with increased risk and which ones might be</p> <p>9 associated with decreased risk.</p> <p>10 Q. To support this statement, did you conduct</p> <p>11 any post-interview interviews?</p> <p>12 A. Can you restate that? Tell me -- I'm not</p> <p>13 sure what you're asking.</p> <p>14 Q. So to determine if study hypotheses were</p> <p>15 known to the study subjects at the time that they were</p> <p>16 asked the questions, there would be methods or ways to</p> <p>17 which you could find that out; correct?</p> <p>18 A. We -- I'm thinking about it. I have never</p> <p>19 known that to be -- I've never known a study that has</p> <p>20 done that.</p> <p>21 In one breast cancer study, at the end of</p> <p>22 the interview, we asked the women if they had any</p> <p>23 ideas about what caused breast cancer. And, you know,</p> <p>24 we thought it might maybe raise some new ideas, but we</p> <p>25 found that it was largely -- we didn't see anything</p>

57 (Pages 222 to 225)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 226</p> <p>1 that was usable. I think that the most common 2 response was that women thought it was stress. So -- 3 Q. But you don't have any evidence of anything 4 similar being done in the talc ovarian cancer 5 literature; correct? 6 A. Not to my knowledge. 7 Q. At the bottom of page 22, and then carrying 8 over through 23, you cite to the Lanza study; correct? 9 A. That's correct. 10 Q. And you cite Lanza for the proposition 11 that -- to provide "further evidence that recall bias 12 in case-control studies does not inevitably lead to an 13 overestimate." 14 Do you see where I was reading? It's at the 15 bottom of 22. 16 A. Yes. Yes, I see where you're reading. 17 Q. Lanza did not pertain to talc and ovarian 18 cancer; correct? 19 A. As I state in my report, yes. It's looking 20 at a variety of meta-analyses that looked at both 21 case-control studies and cohort studies. And the 22 point of that paper was to determine if recall bias 23 seemed to lead to a consistently increased risk. And 24 their conclusion, as I state in here, there's no 25 significant difference in the effect estimates between</p>	<p style="text-align: right;">Page 228</p> <p>1 are that the estimates did not differ between 2 case-control and prospective or retrospective cohort 3 studies; correct? 4 A. Where are you reading, please? 5 Q. I'm in the "Results" section. 6 A. Okay. Yes. 7 Q. And then they say, "Heterogeneity was also 8 low," below that; right? 9 A. Yes. 10 Q. Again, if I'm understanding this paper 11 correctly, the situation for talc and ovarian cancer 12 is completely different, isn't it? Where we do have 13 heterogeneity between the prospective studies and the 14 retrospective case-control studies; right? 15 MS. PARFITT: Objection. Form. 16 THE WITNESS: We have one example in 17 the talc and the -- and the ovarian cancer -- in the 18 meta-analyses, they did note some heterogeneity 19 between the cohort studies and the case-control 20 studies. 21 I think that the point that I was trying to 22 get with that is in the observational studies, there's 23 always concern, as several of these people have -- as 24 several of the meta-analyses and other papers have 25 reported, that the stronger association due to --</p>
<p style="text-align: right;">Page 227</p> <p>1 the case-control and cohort studies, suggesting that 2 the study design didn't have an important impact on 3 the conclusions of the meta-analyses. 4 MR. JAMES: Okay. I marked Lanza as 5 Exhibit 27. I'll hand you two copies. 6 (Exhibit No. 27 was marked for identification.) 7 BY MR. JAMES: 8 Q. And so Lanza concerns therapeutic 9 interventions; correct? 10 A. Yes. 11 Q. And isn't -- and correct me if I'm wrong 12 here, but looking at Lanza, isn't what Lanza doing is 13 they're comparing the odds ratios reached in both the 14 case-control studies and in the prospective studies on 15 a completely different body of literature; right? 16 A. It is not dealing with talc and ovarian 17 cancer, if that is your question. 18 Q. And they're looking at whether the results of 19 the case-control studies on that separate body of 20 literature and the results of the prospective cohort 21 studies on that separate body of literature reached 22 different results; right? 23 A. Yes. 24 Q. Okay. And so the author's conclusions in the 25 abstract here are -- which you note in your report --</p>	<p style="text-align: right;">Page 229</p> <p>1 among the case-control studies was due to some kind of 2 recall bias. 3 So the point is, if it was recall bias, you 4 would expect to see that case-control studies always 5 had higher estimates than the cohort studies; and this 6 study is making the point that in this wide variety of 7 interventions that they looked at, that doesn't seem 8 to be the case at all. Okay. 9 BY MR. JAMES: 10 Q. So, again, this study is saying, "Look, the 11 results of case-control studies and the results of 12 prospective cohort studies on these therapeutic 13 interventions are similar, same ballpark, and so thus, 14 we can conclude that recall bias in this body of 15 literature must not be a big deal." 16 Is that a layman's fair way to describe the 17 results of this paper? 18 MS. PARFITT: Objection. Form. 19 THE WITNESS: Yeah. I -- I mean, 20 I think that it's one part of the -- I think that, 21 overall, that's a pretty fair summary of the point 22 that this paper is making. So... 23 BY MR. JAMES: 24 Q. And if you acknowledge that in the talc 25 ovarian cancer literature, there is a disparity</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 230	Page 232
<p>1 between the retrospective case-control studies and the 2 prospective cohort studies, then Lanza isn't really 3 applicable at all, is it? 4 MS. PARFITT: Objection. 5 THE WITNESS: It is -- I think that it 6 is very applicable because it's trying to get at the 7 recall -- is recall bias -- is that a problem in 8 case-control studies that is going to inevitably lead 9 to higher risk estimates than what you would get in 10 cohort studies? 11 And as we have seen in these articles, we 12 see recall bias is frequently cited as a potential 13 reason that we saw stronger associations in 14 case-control studies than in cohort studies. 15 And I think this paper is really pointing 16 out that that's not inevitable, that you're always 17 going to have higher estimates with case-control 18 studies than cohort studies. 19 Specifically in relation to the 20 heterogeneity between the cohort studies and the 21 case-control studies in talc, I think that we have to 22 consider other biases that may be operating. 23 BY MR. JAMES: 24 Q. I mean, the justification for the Lanza 25 conclusions is that the results in the two study</p>	<p>1 Q. If you're looking at Lanza objectively, 2 doesn't it say exactly the opposite of what you're 3 saying here, Doctor? 4 I mean, again, the justification for Lanza 5 is the results are the same, and so recall bias isn't 6 a problem. But that justification doesn't exist in 7 the world of talc ovarian cancer. 8 That will be my last question on that. 9 A. No. I think that this addresses the recall 10 bias in the -- you know, I acknowledge it doesn't 11 directly address talc and ovarian cancer in this 12 paper; but it does address this -- this commonly-cited 13 thing that, you know, recall bias in case-control 14 studies could lead to higher risk estimates. And it's 15 saying that's not necessarily the case always. 16 Q. I promised that was my last question -- 17 A. Okay. 18 Q. -- so we'll move on. 19 The third factor that you discuss as a 20 particular threat for recall bias is if there is 21 considerable media attention. 22 Do you see where I've returned back to on 23 page 22? 24 21 is where you -- 21 through 22 is where 25 you lay out the three reasons. At the top of 22, you</p>
Page 231	Page 233
<p>1 designs are pretty much the same. So these two study 2 designs didn't reach different results. And so in 3 this body of literature, we don't really need to be 4 worried about recall bias. Recall bias was not 5 operating to create a disparity of results in this 6 body of literature. 7 But, in contrast, in the talc ovarian cancer 8 world, there is a disparity in the results by study 9 design; right? 10 A. We've already acknowledged there is some 11 heterogeneity in results. Is it due to recall bias? 12 Is it -- do we have to assume that recall bias is in 13 play here and that explains the higher -- or the 14 stronger associations generally reported in the 15 case-control studies. 16 And this article is addressing one -- one 17 potential bias, the recall bias. And I don't -- 18 I think that it provides support that we cannot just 19 do a knee-jerk reaction of "case-control studies, they 20 have the potential for recall bias, that leads to 21 higher estimates, and therefore, these studies are 22 biased." 23 There are other biases in play in the cohort 24 studies that I think are very plausible explanations 25 for why there might be some differences.</p>	<p>1 say "considerable media attention." 2 A. Yes. 3 Q. And then you evaluate the media attention 4 factor on the following page; right? 5 A. On page 23, yes. 6 Q. On 23, you say that, for the media attention 7 concern, you say in the middle of the first full 8 paragraph (as read): 9 "The concern is not relevant to 10 the vast majority of the studies 11 as virtually all the data 12 collection in the epidemiologic 13 studies of talc and ovarian cancer 14 occurred prior to such 15 litigation." 16 Do you see that? 17 A. Yes, I do. 18 Q. And you agree that media attention is not 19 limited to litigation; correct? 20 A. Yes. 21 Q. Did you undertake any effort to analyze the 22 extent of publicity or media attention to the talc 23 ovarian cancer issue prior to 2014? 24 A. I did not do any specific analysis of that. 25 I personally was unaware of any media attention on</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 234	Page 236
<p>1 this topic prior to the litigation.</p> <p>2 Q. Then I believe on page 23, you go on to</p> <p>3 discuss the Schildkraut 2016 paper; correct?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. And if we can pull that back out. It</p> <p>6 is the exhibit -- did I mark it?</p> <p>7 MS. PARFITT: I don't think so.</p> <p>8 MR. JAMES: Okay. I'll mark it as the</p> <p>9 next one, so you don't have to fish for it here. It's</p> <p>10 Exhibit 28.</p> <p>11 (Exhibit No. 28 was marked for identification.)</p> <p>12 MR. JAMES: Which is the Schildkraut</p> <p>13 2016 paper. I'll hand you two copies.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. And so we touched upon this a bit earlier,</p> <p>16 Dr. Moorman, where we talked about the phraseology</p> <p>17 where you say the association was "attenuated but not</p> <p>18 eliminated."</p> <p>19 Do you recall that exchange we had earlier?</p> <p>20 THE WITNESS: Yes, I do.</p> <p>21 BY MR. JAMES:</p> <p>22 Q. Okay. And in this 2016 paper, again, you,</p> <p>23 among the authors, compared the odds ratios for talc</p> <p>24 and ovarian cancer for participants before 2014 and</p> <p>25 for participants after 2014; correct?</p>	<p>1 Q. And you -- I believe this table reflects --</p> <p>2 though I'm still looking for it, and maybe you can</p> <p>3 help me with it -- but the data in this table reflects</p> <p>4 that pre-2014 interviewees reported talc usage at the</p> <p>5 rate of 36 percent, and post-2014 interviewees</p> <p>6 reported rates -- excuse me, reported usage at the</p> <p>7 rate of 51 percent.</p> <p>8 A. Yes, I see that in the table.</p> <p>9 Q. And so that's a significant disparity in</p> <p>10 reported usage rates; would you agree with that?</p> <p>11 MS. PARFITT: Objection. Form.</p> <p>12 THE WITNESS: Clearly, it is what it</p> <p>13 is. It's 36 percent as -- versus 51 percent. Okay.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. And so we have your paper here showing that</p> <p>16 before 2014, before the onset of the litigation, you</p> <p>17 had study participants reporting talc usage at a lower</p> <p>18 rate; right?</p> <p>19 A. Than -- yes.</p> <p>20 Q. And if you isolated the association analysis</p> <p>21 to those -- to that group, you also have a</p> <p>22 non-statistically significant association; correct?</p> <p>23 A. And again, when you stratify -- we've already</p> <p>24 covered that. I acknowledge that prior to 2014, it</p> <p>25 was not statistically significant. We also indicated</p>
Page 235	Page 237
<p>1 A. Correct.</p> <p>2 Q. And if we look at page 1414 -- I'm looking</p> <p>3 for my place here.</p> <p>4 If you look at Table 2, Dr. Moorman, you see</p> <p>5 there where you have broken out the data on interview</p> <p>6 date after 2014; right?</p> <p>7 A. Yes.</p> <p>8 Q. And then above that is the interview date</p> <p>9 before 2014; correct?</p> <p>10 A. Yes.</p> <p>11 Q. And we see that the odds ratio here for</p> <p>12 interview date after 2014 is 2.91; correct?</p> <p>13 A. That is correct.</p> <p>14 Q. That's well in excess of any odds ratio</p> <p>15 reported in any of the meta-analyses; correct?</p> <p>16 A. For the overall summary odds ratio, yes.</p> <p>17 Q. And before 2014, we see that the odds ratio</p> <p>18 is a 1.19 that is not statistically significant, which</p> <p>19 is what we discussed earlier; correct?</p> <p>20 A. Yes, we discussed that earlier.</p> <p>21 Q. And you also report in this article a</p> <p>22 distinction between the pre-2014 interviewees and the</p> <p>23 post-2014 interviewees based upon their reported talc</p> <p>24 usage; right?</p> <p>25 A. Yes.</p>	<p>1 certainly in the range of what many other studies have</p> <p>2 seen. But when you stratify like that, you are</p> <p>3 getting into smaller sample sizes. So there's</p> <p>4 statistical significance that -- the fact that it's no</p> <p>5 longer statistically significant is not all that</p> <p>6 surprising.</p> <p>7 Q. Have you seen the Trabert editorial that</p> <p>8 followed the publication of the Schildkraut article?</p> <p>9 A. I'm sure that I have read it at some point,</p> <p>10 but --</p> <p>11 Q. Okay. I'm going to -- I'm sorry.</p> <p>12 A. -- please, let's -- I haven't looked at it in</p> <p>13 quite some time.</p> <p>14 Q. So I'm going to mark as Exhibit 29 an</p> <p>15 editorial by Britton Trabert entitled "Body Powder and</p> <p>16 Ovarian Cancer Risk -- What is the Role of Recall</p> <p>17 Bias?"</p> <p>18 I'll hand you two copies.</p> <p>19 (Exhibit No. 29 was marked for identification.)</p> <p>20 BY MR. JAMES:</p> <p>21 Q. Dr. Moorman, does this editorial look</p> <p>22 familiar to you? Have you seen it before?</p> <p>23 A. Yes, I have seen it before.</p> <p>24 Q. Have you ever spoken with or communicated</p> <p>25 with Britton Trabert about this editorial?</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 238	Page 240
<p>1 A. No, I have not.</p> <p>2 Q. And you see that in the right-hand column,</p> <p>3 about midway down, Dr. Trabert refers to the data</p> <p>4 points that we were just discussing; correct?</p> <p>5 A. Yes.</p> <p>6 Q. And if you look to the second page of the</p> <p>7 editorial, Trabert reports, at the last paragraph of</p> <p>8 the article (as read):</p> <p>9 "The current study highlights the</p> <p>10 concern over recall bias in</p> <p>11 case-control studies, particularly</p> <p>12 once an exposure becomes the</p> <p>13 subject of considerable media</p> <p>14 coverage."</p> <p>15 Do you see where I was reading that?</p> <p>16 A. Yes, I do.</p> <p>17 Q. Do you agree with Dr. Trabert's concerns</p> <p>18 about media coverage impacting the results of the</p> <p>19 Schildkraut study?</p> <p>20 A. I -- I think that the investigators on our</p> <p>21 study, they had that concern. That's why we did those</p> <p>22 analyses. So...</p> <p>23 Q. So do you acknowledge the possibility that</p> <p>24 the results of the 2016 study may reflect recall bias</p> <p>25 in the study?</p>	<p>1 possibility of recall bias, but I think that we looked</p> <p>2 at the other side of the coin as well.</p> <p>3 Q. And can you tell me where you're reading that</p> <p>4 sentence from, Dr. Moorman?</p> <p>5 A. Let's see. The -- it is on page 1416, the</p> <p>6 right-hand column, and it's about -- probably about</p> <p>7 eight or nine lines down.</p> <p>8 So I think that this sentence -- or this</p> <p>9 whole paragraph gives a pretty balanced assessment of</p> <p>10 the data, that we thoughtfully considered the issue of</p> <p>11 recall bias, but we also considered that maybe the</p> <p>12 greater publicity led to -- was kind of a memory</p> <p>13 trigger that led to more accurate recall.</p> <p>14 Q. And in your report, do you include a caution</p> <p>15 on the Schildkraut 2016 study about the potential for</p> <p>16 recall bias based upon the 2014 pre- and post-data?</p> <p>17 A. I -- let's see. We have discussed that</p> <p>18 section of the report a couple of times already. And</p> <p>19 I state that there is the possibility that recall bias</p> <p>20 could have led to the higher odds ratios when</p> <p>21 including women interviewed during the time when there</p> <p>22 was more media attention focused on this exposure.</p> <p>23 Q. And you're at page 23; right?</p> <p>24 A. Yes.</p> <p>25 Q. Okay. And then you conclude the middle</p>
Page 239	Page 241
<p>1 A. In this discussion -- if I may take just a</p> <p>2 moment to --</p> <p>3 Q. Certainly.</p> <p>4 A. Okay. You know, I think that</p> <p>5 Dr. Schildkraut, who did the major writing of this</p> <p>6 article -- and I think all of the coauthors were in</p> <p>7 agreement -- that we were concerned about the recall</p> <p>8 bias. As I said, that was some of the reason for</p> <p>9 doing those analyses.</p> <p>10 I think that it's also important to point</p> <p>11 out here the other possibility. There may have been</p> <p>12 some recall bias. But she also makes the statement</p> <p>13 that (as read):</p> <p>14 "It is possible that the lawsuit</p> <p>15 sharpened memories of body powder</p> <p>16 use and improved the accuracy of</p> <p>17 reported use for both cases and</p> <p>18 controls interviewed in 2014 or</p> <p>19 later."</p> <p>20 I think that that goes to say that anytime</p> <p>21 someone -- you know, there's some memory trigger, it</p> <p>22 could have made actually more accurate recall.</p> <p>23 So we --</p> <p>24 Q. And Dr. --</p> <p>25 A. I'm sorry. So we acknowledge both the</p>	<p>1 paragraph with the statement that -- the "attenuated</p> <p>2 but not eliminated" statement. But I'm not going to</p> <p>3 ask about that again. But you go on in that sentence</p> <p>4 to say (as read):</p> <p>5 "The association is not due</p> <p>6 entirely to recall bias."</p> <p>7 Do you see that phrasing that I just read?</p> <p>8 A. Yes.</p> <p>9 Q. So are you conveying in that wording that you</p> <p>10 think some portion of the odds ratio that you are</p> <p>11 seeing in these case-control studies that you're</p> <p>12 relying on or the meta-analyses that you're relying</p> <p>13 on, that some portion of that odds ratio is</p> <p>14 attributable to recall bias?</p> <p>15 MS. PARFITT: Objection.</p> <p>16 THE WITNESS: I think that probably</p> <p>17 every meta-analysis published, probably every</p> <p>18 case-control study that was published, we acknowledge</p> <p>19 this as a -- recall bias is a potential bias. But</p> <p>20 I think that we went on to give evidence --</p> <p>21 I explained why I did not think that it was a complete</p> <p>22 explanation.</p> <p>23 Can we completely rule out any possibility</p> <p>24 of recall bias? I don't know that we can do it. But</p> <p>25 I think that as -- for some of the reasons</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 242</p> <p>1 I articulated.</p> <p>2 I know that Dan Cramer in his 2016 paper</p> <p>3 also went into great detail considering the issue of</p> <p>4 recall bias. And I don't think that we can attribute</p> <p>5 this association to recall bias.</p> <p>6 BY MR. JAMES:</p> <p>7 Q. Can you cite to any publication that has</p> <p>8 analyzed the literature and ruled out recall bias --</p> <p>9 MS. PARFITT: Objection.</p> <p>10 BY MR. JAMES:</p> <p>11 Q. -- as a method -- as a basis for the elevated</p> <p>12 odds ratio of the 1.2 to 1.3 that you're citing in</p> <p>13 your report?</p> <p>14 MS. PARFITT: Objection.</p> <p>15 THE WITNESS: Okay. I went back to the</p> <p>16 Dan Cramer article, and I'm hoping that I'm recalling</p> <p>17 that particular article, the date of it, accurately.</p> <p>18 But he did analyze the data and the degree of</p> <p>19 misclassification that would have had to occur for</p> <p>20 recall bias to account for this association. He gave</p> <p>21 other reasons for why it seemed unlikely that recall</p> <p>22 bias would account for this association.</p> <p>23 So I think he did a pretty thorough</p> <p>24 analysis -- a thoughtful analysis of it.</p> <p>25</p>	<p style="text-align: right;">Page 244</p> <p>1 Q. Okay. Dr. Moorman, on page 11 of your</p> <p>2 report, you talk about -- this is where you begin your</p> <p>3 analysis of the Bradford Hill factors.</p> <p>4 A. Yes.</p> <p>5 Q. And are you there with me?</p> <p>6 A. Yes, I am.</p> <p>7 Q. Okay. You say, in page 11 -- you have a</p> <p>8 section titled "Strength and consistency of the</p> <p>9 association"; correct?</p> <p>10 A. Correct.</p> <p>11 Q. You say in the first sentence that strength</p> <p>12 and consistency are "deeply intertwined." Correct?</p> <p>13 A. Yes.</p> <p>14 Q. Can you cite to any publication where you</p> <p>15 have combined the analysis of strength and consistency</p> <p>16 before?</p> <p>17 A. I -- I can't cite any publication that</p> <p>18 specifically addresses that, no.</p> <p>19 Q. Can you cite any published authority that</p> <p>20 states these two Bradford Hill criteria are deeply</p> <p>21 intertwined?</p> <p>22 A. I -- I think that as I was -- I cannot cite a</p> <p>23 published authority.</p> <p>24 I think that, again, this is based on when</p> <p>25 I was looking at these and how I was weighting these</p>
<p style="text-align: right;">Page 243</p> <p>1 BY MR. JAMES:</p> <p>2 Q. Can you cite any other publications other</p> <p>3 than the Cramer 2016 paper, sitting here today, that</p> <p>4 have addressed recall bias in the fashion that you</p> <p>5 just described?</p> <p>6 A. The Cramer article is the one that I -- that</p> <p>7 comes to mind as the one that addressed it most</p> <p>8 thoroughly.</p> <p>9 Q. Have you ever published the three factors</p> <p>10 that you have addressed with regard to recall bias?</p> <p>11 A. The three factors are --</p> <p>12 Q. Sure. So --</p> <p>13 A. Okay.</p> <p>14 Q. Within your report, you -- we just walked</p> <p>15 through the three factors that you've considered, the</p> <p>16 three factors that you deemed to be a particular</p> <p>17 threat to case-control studies for recall bias;</p> <p>18 correct? We just walked through those three?</p> <p>19 A. Yes.</p> <p>20 Q. Have you ever published those three in any</p> <p>21 article or journal or anything else?</p> <p>22 A. I have not published that. That is just</p> <p>23 based on my general epidemiologic knowledge from doing</p> <p>24 this type of research and teaching in this field for</p> <p>25 the last couple of decades.</p>	<p style="text-align: right;">Page 245</p> <p>1 considerations.</p> <p>2 Q. Do you agree that strength is an important</p> <p>3 criteria in and of itself?</p> <p>4 A. I think that the strength of the association</p> <p>5 is an important criteria, but I think that we also</p> <p>6 have to bear in mind that as -- that there are many</p> <p>7 well-established causal associations that are</p> <p>8 certainly not in the order of magnitude of what we</p> <p>9 see, for example, with smoking and lung cancer.</p> <p>10 Q. Do you think the criteria of strength is met</p> <p>11 with the talc and ovarian cancer literature?</p> <p>12 A. When -- as I go through my report, I give</p> <p>13 numerous examples of well-accepted causal associations</p> <p>14 that are of a similar magnitude as what we see with</p> <p>15 talc and ovarian cancer, and so I think that the data</p> <p>16 are strong enough.</p> <p>17 Q. And I think that I'm going to ask my question</p> <p>18 again.</p> <p>19 A. Okay.</p> <p>20 Q. Do you think that the criteria of strength is</p> <p>21 met with the talc and ovarian cancer literature?</p> <p>22 A. Okay --</p> <p>23 MS. PARFITT: Objection. Asked and</p> <p>24 answered.</p> <p>25 Try again, Dr. Moorman.</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 246</p> <p>1 THE WITNESS: Okay. So, once again, 2 I -- we have to use -- we have to be careful of -- 3 Dr. Hill did not refer to these as "criteria," but 4 guidelines or viewpoints I think was the terminology 5 he used. And I do think that the criteria of strength 6 has been met. 7 BY MR. JAMES: 8 Q. Can you cite to a single study in the talc 9 ovarian cancer literature that refers to the 10 association as a strong association? 11 A. I -- I cannot, off the top of my head, think 12 of anyone that refers to it as a strong association. 13 I do, once again, want to say that we see evidence of 14 causal associations of similar magnitude; so I think 15 that it is strong enough to be a causal association. 16 Q. Do you understand that a number of the papers 17 that you have cited in your reference list or 18 materials-considered list refer to the association as 19 weak? 20 MS. PARFITT: Objection. 21 THE WITNESS: Which papers are you 22 referring to specifically? 23 BY MR. JAMES: 24 Q. If an author in the talc ovarian cancer 25 literature has referred to the association as a weak</p>	<p style="text-align: right;">Page 248</p> <p>1 MR. JAMES: It hasn't been answered. 2 MS. PARFITT: It's been asked. 3 THE WITNESS: I don't think that we 4 have any actual definition of what is modest. I think 5 that the association is what it is, a 25 to 30 percent 6 increased risk. 7 BY MR. JAMES: 8 Q. As an epidemiologist, you're not capable of 9 discerning whether an association is modest or not 10 modest? 11 MS. PARFITT: Objection. 12 THE WITNESS: As I have said before, 13 I don't think there is any clear definition of that 14 adjective. 15 BY MR. JAMES: 16 Q. Is there a definition in the epidemiologic 17 community of a weak association? Are you able to 18 understand what that would mean in the epidemiologic 19 community? 20 A. Once again, there is no -- to my knowledge, 21 there is nothing that would say, you know, an odds 22 ratio in this range is weak, this is modest, this is 23 moderate, this is strong. 24 And, again, going back to Bradford Hill, he 25 certainly emphasizes that there are some associations</p>
<p style="text-align: right;">Page 247</p> <p>1 association, would you agree or disagree with that 2 characterization? 3 MS. PARFITT: Object to form. 4 THE WITNESS: I would disagree with 5 the -- I would disagree with that. 6 BY MR. JAMES: 7 Q. If an author or authors in the talc ovarian 8 cancer literature have referred to the association as 9 modest, would you agree or disagree with that? 10 A. Once again, I think that many of the risk 11 factors that we are considering are not going to be 12 the odds ratios of 10 or greater that we saw with 13 this. 14 And when you read the papers written by 15 Dr. -- by Bradford Hill, he certainly makes the point 16 that some weaker associations can certainly be real. 17 Q. So is this a weaker association? 18 A. Weaker is in comparison to what? It's not -- 19 it's weaker than smoking and lung cancer. It is -- 20 I keep making the point that it -- we fully 21 acknowledge that it is not a tenfold increased risk. 22 It's a 25 to 30 percent increased risk. 23 Q. Would you call the association modest? 24 MS. PARFITT: Objection. Asked and 25 answered.</p>	<p style="text-align: right;">Page 249</p> <p>1 that are not in the magnitude of smoking and lung 2 cancer, but they are certainly real. 3 Q. And I think you're conflating -- or you're 4 misunderstanding my question, because you're answering 5 the question about whether the association is real or 6 not real, and my question for you is whether the 7 association is weak, modest, or strong. 8 How would you characterize it? 9 A. And I would -- as I have said, there is no 10 absolute terminology that would say what is a weak 11 association, what is modest, and what is strong. So 12 I think that it is more accurate just to describe it 13 as it is, a 25 to 30 percent increased risk of ovarian 14 cancer. 15 Q. Well, in assessing the Bradford Hill factors 16 or considerations or criteria -- in assessing that and 17 determining whether the association is strong or not 18 strong, as an epidemiologist, don't you need to be 19 capable of determining whether the association is 20 strong or not strong? 21 A. Once again, it is an adjective that is not 22 well defined. And -- 23 Q. And do you -- I'm sorry. 24 A. I -- I -- I keep going back to I think that 25 the association that we see is what it is, a 25 to</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 250	Page 252
<p>1 30 percent increased risk. It is consistent with</p> <p>2 other factors that we consider causal associations.</p> <p>3 They have a similar strength of association.</p> <p>4 Q. And I do -- I do intend to go to that very</p> <p>5 next topic next --</p> <p>6 A. Okay.</p> <p>7 Q. -- but in assessing strength, what I'm asking</p> <p>8 is whether, in all of the papers that you've cited,</p> <p>9 when the epidemiologists that you've cited refer to</p> <p>10 the association as weak or modest or small, is that</p> <p>11 terminology that you can accept, or is that</p> <p>12 terminology that you reject?</p> <p>13 A. I say that it is terminology that is</p> <p>14 imprecise. What one would consider modest, someone</p> <p>15 else might consider moderate. It's imprecise</p> <p>16 terminology.</p> <p>17 Q. And certainly in the epidemiology world, if</p> <p>18 you have a small or modest or weak association, what</p> <p>19 you're saying is that that doesn't bar a causal</p> <p>20 conclusion. But wouldn't you agree with me that if</p> <p>21 the association is small or modest or weak, it makes</p> <p>22 the other considerations more important?</p> <p>23 MS. PARFITT: Objection.</p> <p>24 THE WITNESS: I think that all of the</p> <p>25 considerations are important. It's --</p>	<p>1 A. Yes.</p> <p>2 Q. And these associations that you've listed,</p> <p>3 you have concluded are generally accepted to be</p> <p>4 causal; correct?</p> <p>5 A. I think so, yes.</p> <p>6 Q. And below that, you state that the IARC has</p> <p>7 reached a causal conclusion with respect to each of</p> <p>8 these associations; is that right?</p> <p>9 A. Yes, that is what I state.</p> <p>10 Q. And so to state that, are you saying that all</p> <p>11 five of these exposures and associations have been</p> <p>12 classified by IARC as Category 1?</p> <p>13 A. I don't recall if -- I don't recall the</p> <p>14 classifications, specifically, for all of these.</p> <p>15 Q. Well, to say that the IARC has made a causal</p> <p>16 judgment on these associations, you are necessarily</p> <p>17 saying that they have classified these associations as</p> <p>18 Category 1; correct?</p> <p>19 A. I -- you know, I answered the question.</p> <p>20 I don't recall which IARC category that each of these</p> <p>21 exposures is right off the top of my head.</p> <p>22 Q. But do you say in the report that they are</p> <p>23 judged to be causal by IARC; correct?</p> <p>24 A. I do say that in my report.</p> <p>25 Q. And IARC has not judged talc ovarian cancer</p>
Page 251	Page 253
<p>1 BY MR. JAMES:</p> <p>2 Q. Do you agree that, with a small association,</p> <p>3 there's more concern for recall bias?</p> <p>4 MS. PARFITT: Objection.</p> <p>5 THE WITNESS: I think that with a</p> <p>6 smaller association, there is more concern that it</p> <p>7 could be due to bias from various reasons.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. Can you cite to any scientific agency or</p> <p>10 organization that has described the talc ovarian</p> <p>11 cancer association as strong?</p> <p>12 A. I do not recall anyone describing it that</p> <p>13 way.</p> <p>14 Q. Okay. And then we will turn now to page 12</p> <p>15 of your report, Dr. Moorman, where you cite a number</p> <p>16 of other exposures.</p> <p>17 A. Yes.</p> <p>18 Q. And do you see where I am?</p> <p>19 A. Yes.</p> <p>20 Q. And you say on page 12 that (as read):</p> <p>21 "Well-accepted exposure to these</p> <p>22 associations have relative risks</p> <p>23 of similar magnitude and are</p> <p>24 generally accepted to be causal."</p> <p>25 Do you see where I was reading?</p>	<p>1 to be a causal association, has it?</p> <p>2 A. As we have discussed several times today,</p> <p>3 they describe it as possibly carcinogenic.</p> <p>4 Q. Can you cite to any publication that assesses</p> <p>5 the strength of an epidemiologic association by</p> <p>6 considering "similar magnitude" odds ratios from</p> <p>7 unrelated exposures to diseases?</p> <p>8 A. I -- off the top of my head, I can't cite any</p> <p>9 such publication.</p> <p>10 Q. Have any scientific agencies that have looked</p> <p>11 at this issue assessed strength of the talc ovarian</p> <p>12 cancer relationship by considering similar magnitude</p> <p>13 associations of unrelated exposures to diseases?</p> <p>14 A. I know that in the Health Canada report, they</p> <p>15 went through assessing the strength of the</p> <p>16 association. I don't recall if they kind of</p> <p>17 considered it in relation to other exposures that have</p> <p>18 a similar magnitude of association.</p> <p>19 Q. With regard to the associations that you have</p> <p>20 identified on page 12, did you review the entire body</p> <p>21 of scientific and medical literature pertaining to</p> <p>22 those associations?</p> <p>23 A. In -- let's see. Since when I cited these,</p> <p>24 I did not go through the same level of detail like</p> <p>25 I have done for the talc and ovarian cancer.</p>

64 (Pages 250 to 253)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 254	Page 256
<p>1 The oral contraceptive use and breast cancer 2 that I cite, I was part of a team of researchers that 3 did a systematic review and meta-analysis of oral 4 contraceptives in relation to ovarian cancer as well 5 as breast cancer and some other cancers. 6 The other ones, again, I did not go in -- 7 did not review the body of literature in the same 8 detail as I did the talc and ovarian cancer. 9 Q. Did you assess, in any of these bodies of 10 literature, the risks for recall bias? 11 A. I did not. 12 Q. Did you consider, in these bodies of 13 literature, biologic mechanism for these five 14 exposures that you've identified? 15 A. I considered biologic mechanism, again, not 16 in the level of detail with the talc and ovarian 17 cancer. 18 Q. Did you assess them in a manner sufficient to 19 which you would opine in a published article or a 20 litigation report about the evidence supporting 21 causation? 22 A. I'm reading your question again. 23 Q. So am I. 24 A. I'm not sure. 25 Q. For these five exposures and diseases that</p>	<p>1 BY MR. JAMES: 2 Q. So in your report, when you are assessing 3 strength, and you discuss the fact that there are 4 similar magnitude odds ratios from other exposures 5 upon which one could conclude causation, you do not 6 also remark that there are similar magnitude ratios 7 upon one which could not conclude causation. 8 Why is that? Why did you lay out the 9 analysis this way? 10 A. What I was trying to do here is to make the 11 point that an association in the range of a 25 to 12 30 percent increased risk is something that there are 13 multiple examples of this being generally accepted as 14 a causal association. 15 I -- it was not my intent to describe the 16 entire universe of exposures and some that might be in 17 this range. 18 Q. There are certainly examples that you didn't 19 cite in the 1.2 to 1.3 range that are not causal; 20 right? 21 A. Did you have something specific in mind that 22 you are -- 23 Q. I'm asking you, actually. 24 Did you just go searching for similar 25 magnitude ratios upon which one could reach a</p>
Page 255	Page 257
<p>1 you've cited on page 12, did you assess the body of 2 scientific and medical literature and evidence in a 3 manner sufficient to which you would feel comfortable 4 offering an opinion in the published literature or in 5 a litigation report about causation? 6 A. I think that I have answered the question 7 repeatedly that I did not do it in the detail that 8 I did the talc and ovarian cancer. If I were to put 9 in published literature or a litigation report, 10 I would want to make sure that I had done it as 11 absolutely thoroughly as possible. 12 Q. Your comparison of the odds ratios to these 13 five exposures -- you acknowledge that there are 14 exposures that you have not identified in your report 15 that are in the 1.2 to 1.3 range that are not causal 16 or have not proven to be causal; correct? 17 MS. PARFITT: Objection. Form. 18 THE WITNESS: I acknowledge that -- of 19 course, that there are reports of exposures that have 20 reported relative risk in this range, and it could 21 either be something that was associated with another 22 risk factor and it was not the causal factor or the 23 level of evidence was not adequate. Maybe people -- 24 there were fewer articles, people have not gone 25 through the whole evaluation of the causal criteria.</p>	<p>1 causation conclusion? 2 A. I -- I think that I was trying to get at that 3 is this association strong enough to be causal? And 4 we have evidence from these other exposures that, yes, 5 it's certainly possible. 6 The point is that you do not -- or you do 7 not dismiss an association of 1.25 or 1.3 as it 8 couldn't possibly be causal. We have evidence to 9 suggest that it -- there are many examples of it. 10 Q. But in your report, Dr. Moorman, you're not 11 just not dismissing it. You're not just using the 12 similar magnitude odds ratios to not dismiss the 13 possibility that this is a real association. You're 14 using the similar magnitude ratios in an effort to 15 ascribe strength to the association; correct? 16 A. Right. I am saying that I think this is 17 strong enough to be a real association, and I think 18 that we have other examples of similar magnitude 19 associations that are generally accepted as causal 20 associations. 21 Q. But if there are other odds ratios for other 22 exposures to diseases that you did not identify in 23 your report in the 1.2 to 1.3 range that are not 24 causal, then the magnitude ratio that you have here in 25 the top ovarian cancer literature, in that instance,</p>

65 (Pages 254 to 257)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 258	Page 260
<p>1 is not strong enough to support causation?</p> <p>2 MS. PARFITT: Objection. Form.</p> <p>3 BY MR. JAMES:</p> <p>4 Q. I'll just restate it because it's confusing.</p> <p>5 A. Yeah, it is.</p> <p>6 Q. To support strength in your report, why do</p> <p>7 you select only similar magnitude ratios that, by your</p> <p>8 estimation, are Category 1 -- by your estimation, have</p> <p>9 been declared by IARC to be causal associations? Why</p> <p>10 do you only select associations by which one has -- by</p> <p>11 which IARC has concluded causation? Why don't you</p> <p>12 also acknowledge that there are associations of a</p> <p>13 similar magnitude that don't support causation?</p> <p>14 MS. PARFITT: Objection.</p> <p>15 THE WITNESS: I'm not really sure --</p> <p>16 I'm still not really sure what you're getting at with</p> <p>17 this question.</p> <p>18 I think that I was trying to make the point</p> <p>19 that the association we see here is strong enough to</p> <p>20 be accepted as a causal association. I'm not -- I'm</p> <p>21 not saying that every association of this magnitude</p> <p>22 has gone through the same process of assessing all of</p> <p>23 the Bradford Hill viewpoints and have come to the same</p> <p>24 conclusion, but I am saying that we have multiple</p> <p>25 examples of where an association of this magnitude is</p>	<p>1 Do you see where I'm reading that?</p> <p>2 A. Yes.</p> <p>3 Q. There, are you referring to epidemiologic</p> <p>4 literature?</p> <p>5 A. What -- you're taking one sentence and --</p> <p>6 I think that I discussed what I considered related to</p> <p>7 the passive smoke exposure and lung cancer and</p> <p>8 described it in more detail on page 13, the first full</p> <p>9 paragraph.</p> <p>10 Q. And is it fair to say that that body of</p> <p>11 evidence that you're referring to there is the</p> <p>12 epidemiologic literature?</p> <p>13 A. Yes.</p> <p>14 Q. You're not referring there to any sort of</p> <p>15 mechanistic studies or plausibility studies or</p> <p>16 anything like that; correct?</p> <p>17 A. No. I was looking at -- basically, I was</p> <p>18 comparing the two -- or the meta-analyses for the two</p> <p>19 topics.</p> <p>20 Q. On page 14, Dr. Moorman, you discuss the</p> <p>21 "prevalence of exposure."</p> <p>22 Do you see where I am? It's the --</p> <p>23 A. It's about halfway down?</p> <p>24 Q. Yeah, second full paragraph.</p> <p>25 A. Yes.</p>
Page 259	Page 261
<p>1 causal.</p> <p>2 MS. PARFITT: Scott, is this a breaking</p> <p>3 point or no?</p> <p>4 MR. JAMES: How long have we been</p> <p>5 going?</p> <p>6 MR. FARIES: About an hour and 15.</p> <p>7 MS. BRENNAN: Yeah, we've been going</p> <p>8 about an hour and 15.</p> <p>9 MR. JAMES: Sure. Are we ready for a</p> <p>10 break?</p> <p>11 MS. PARFITT: Sure. Just a short one,</p> <p>12 yeah. Thank you.</p> <p>13 THE VIDEOGRAPHER: Going off the record</p> <p>14 at 4:33 p.m.</p> <p>15 (Recess taken from 4:33 p.m. to 4:46 p.m.)</p> <p>16 THE VIDEOGRAPHER: Back on record at</p> <p>17 4:47 p.m.</p> <p>18 BY MR. JAMES:</p> <p>19 Q. Dr. Moorman, on page 13 to 14 of your report,</p> <p>20 and really the top of page 14, you have a sentence</p> <p>21 stating that (as read):</p> <p>22 "The evidence for talc and ovarian</p> <p>23 cancer is as significant as for</p> <p>24 passive smoke exposure and lung</p> <p>25 cancer."</p>	<p>1 Q. And you say that it's critical to consider</p> <p>2 the prevalence of exposure in conjunction with</p> <p>3 considering strength; correct?</p> <p>4 A. I say (as read):</p> <p>5 "It's critical to consider the</p> <p>6 prevalence of the exposure in the</p> <p>7 population when evaluating its</p> <p>8 public health impact."</p> <p>9 Q. Before that, you say "in conjunction with the</p> <p>10 strength of the association." Right?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. Do you think that the prevalence of</p> <p>13 exposure in the population, that that impacts your</p> <p>14 analysis on whether an association is strong or not</p> <p>15 strong?</p> <p>16 A. I think that the way that I stated it here</p> <p>17 is, you know, as an epidemiologist, a public health</p> <p>18 professional, I'm interested in the public health</p> <p>19 impact and how many cases of disease could be</p> <p>20 attributable to this exposure.</p> <p>21 So I go through and describe that factor</p> <p>22 that has a stronger association but is less common in</p> <p>23 the population could have potentially less public</p> <p>24 health impact than a risk factor that is -- doesn't</p> <p>25 have as high an odds ratio but you have many more</p>

66 (Pages 258 to 261)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 262	Page 264
<p>1 exposed people in the population.</p> <p>2 Q. Moving on to consistency, Dr. Moorman, is</p> <p>3 consistency met on this body of literature?</p> <p>4 A. I do feel that consistency is met.</p> <p>5 Q. And on page 14, you -- I think it's page 14.</p> <p>6 Yes. In the first full paragraph, you discuss your --</p> <p>7 you see the last sentence of that paragraph, where you</p> <p>8 say (as read):</p> <p>9 "This observation has been quite</p> <p>10 consistent with findings</p> <p>11 replicated in studies conducted by</p> <p>12 different teams of investigators</p> <p>13 in different geographic locations</p> <p>14 and different race ethnic groups</p> <p>15 over a span of several decades."</p> <p>16 Do you see that?</p> <p>17 A. Yes, I do.</p> <p>18 Q. Is that reflective of -- is that the basis</p> <p>19 upon which you conclude consistency is met?</p> <p>20 A. It is part of the basis of it. I think that,</p> <p>21 when we look at the overall meta-analyses, we look at</p> <p>22 the direction of the effect in all the studies and of</p> <p>23 these, like, 27 different studies, like, 90 percent of</p> <p>24 them show an increased -- or an odds ratio greater</p> <p>25 than 1.</p>	<p>1 cancer?</p> <p>2 A. They -- if we can go back to them, we see</p> <p>3 that there are multiple studies from the Nurses'</p> <p>4 Health Study, and then the Houghton study. They are</p> <p>5 showing a relative risk in most cases, I think, 1.12</p> <p>6 to 1.19. And, again, we have discussed some of the</p> <p>7 biases that might result in an attenuation of the</p> <p>8 association.</p> <p>9 And so I acknowledge that, with the</p> <p>10 exception of the serous invasive cancer in one of the</p> <p>11 studies, the associations have not been statistically</p> <p>12 significant, but they are certainly kind of in the</p> <p>13 direction of -- as the case-control studies.</p> <p>14 Q. Doctor, let's turn back briefly to the</p> <p>15 Houghton study. It's Exhibit 25.</p> <p>16 Are you with me?</p> <p>17 Dr. Moorman, if we look at the Houghton</p> <p>18 study on the first page in the results section of the</p> <p>19 abstract. Do you see where I'm looking?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. The authors there, they report</p> <p>22 every-use odds ratio as a 1.06.</p> <p>23 Do you see that?</p> <p>24 A. I do see that --</p> <p>25 Q. Okay. I'm running out of time, Dr. Moorman,</p>
Page 263	Page 265
<p>1 When we look at epidemiologic data, for</p> <p>2 reasons that we have discussed earlier today, it is</p> <p>3 very uncommon for every single study to reach the same</p> <p>4 conclusion. Some are going to have higher risk; some</p> <p>5 are going to be lower risk. And the level of</p> <p>6 consistency seen here, where virtually every study is</p> <p>7 showing an odds ratio greater than 1, I consider that</p> <p>8 quite consistent.</p> <p>9 Q. You understand that Bradford Hill, when he</p> <p>10 describes consistency, he talks about consistency</p> <p>11 across study design.</p> <p>12 Were you aware of that?</p> <p>13 A. Yes, I am. And I actually do -- the way that</p> <p>14 I described consistency, where even, you know -- two</p> <p>15 of the three cohort studies -- and we've already</p> <p>16 discussed the concerns I have about the Sister Study,</p> <p>17 which is really quite an outlier when we look at this</p> <p>18 whole body of literature. But both the Houghton study</p> <p>19 and the Nurses' Health Study, they are consistent in</p> <p>20 terms of the direction of the effect. And we have</p> <p>21 discussed the statistical significance at all.</p> <p>22 But in terms of the direction of the effect,</p> <p>23 I think that it is consistent.</p> <p>24 Q. So is your position that the cohorts</p> <p>25 demonstrate an association between talc and ovarian</p>	<p>1 so I really am going to ask you to answer my precise</p> <p>2 question.</p> <p>3 Do you see where the authors, they say</p> <p>4 there -- the authors say that it's "not associated</p> <p>5 with risk of ovarian cancer compared with never-use."</p> <p>6 Do you see that?</p> <p>7 A. Yes, that is what they state.</p> <p>8 Q. Okay. And 1.06 is -- again, it's not a</p> <p>9 statistically significant association; correct?</p> <p>10 A. With the confidence interval that they</p> <p>11 report. That's what tells you whether or not it's</p> <p>12 statistically significant. And with that confidence</p> <p>13 interval, no, it is not statistically significant.</p> <p>14 Q. And it's also very close to the null, isn't</p> <p>15 it?</p> <p>16 A. Yes. It's the 1.06, yes.</p> <p>17 Q. And the conclusion of the authors here is</p> <p>18 that (as read):</p> <p>19 "Perineal powder use does not</p> <p>20 appear to influence ovarian cancer</p> <p>21 risk."</p> <p>22 Correct?</p> <p>23 A. That's what they state, yes.</p> <p>24 Q. So this is one of the cohorts that you're</p> <p>25 talking about today; correct?</p>

67 (Pages 262 to 265)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 266	Page 268
<p>1 A. Right. And --</p> <p>2 Q. And the authors here conclude that there's</p> <p>3 not an association between ovarian cancer risk and</p> <p>4 perineal talc use, don't they?</p> <p>5 MS. PARFITT: Objection. Form.</p> <p>6 THE WITNESS: Okay. Yes, I acknowledge</p> <p>7 that's their conclusion. And I think that -- I'm</p> <p>8 sorry -- the data that I was referring to comes from</p> <p>9 Table 3. And I, again, acknowledge that it was not</p> <p>10 statistically significant, but he said only genital</p> <p>11 powder use -- which is mostly what we're</p> <p>12 considering -- it had a hazard ratio of 1.4 or 1.3 --</p> <p>13 I'm sorry -- 1.14 or 1.13.</p> <p>14 And so, again, it's in the direction of</p> <p>15 effect, and, as we have discussed, biases could have</p> <p>16 led to some attenuation.</p> <p>17 BY MR. JAMES:</p> <p>18 Q. Are you saying that you believe that there's</p> <p>19 consistency among -- or between the case-control</p> <p>20 studies and the cohort studies in the talc ovarian</p> <p>21 cancer literature?</p> <p>22 A. I am saying that -- as I have pointed out</p> <p>23 here and with also the Nurses' Health Study, I am</p> <p>24 saying that there is consistency in the direction of</p> <p>25 the effect that they observed, and acknowledging that</p>	<p>1 right around 1. About half the studies have odds</p> <p>2 ratios greater than 1; about half have odds ratios</p> <p>3 less than 1. So in that case, I would say there is no</p> <p>4 consistency.</p> <p>5 I contrast it with this where, when you look</p> <p>6 at the forest plots from the meta-analyses, nearly all</p> <p>7 of the studies have odds ratios greater than 1.</p> <p>8 BY MR. JAMES:</p> <p>9 Q. And you're including in that testimony the</p> <p>10 cohort studies?</p> <p>11 A. Yes.</p> <p>12 Q. Odds ratios that are not statistically</p> <p>13 significant, in your mind, demonstrate consistency</p> <p>14 by -- among study design. Is that your testimony?</p> <p>15 MS. PARFITT: Objection. Form.</p> <p>16 THE WITNESS: I'm sorry --</p> <p>17 BY MR. JAMES:</p> <p>18 Q. Your testimony here today is that the results</p> <p>19 reached by the cohort studies and the case-control</p> <p>20 studies are consistent. Is that your testimony?</p> <p>21 A. My testimony, as I have stated repeatedly,</p> <p>22 that there is a great deal of consistency in the</p> <p>23 direction of the effect, that nearly all of the</p> <p>24 studies report an odds ratio greater than 1. And</p> <p>25 I acknowledge that not all studies are statistically</p>
Page 267	Page 269
<p>1 these were not statistically significant findings.</p> <p>2 Q. So even though the authors report that</p> <p>3 there's not an association, you're claiming today that</p> <p>4 the cohort studies are consistent with the</p> <p>5 case-control studies in finding a association?</p> <p>6 MS. PARFITT: Objection. Form.</p> <p>7 THE WITNESS: I think that I have</p> <p>8 answered the question already that, in terms of the</p> <p>9 direction of the effect, that the Houghton study for</p> <p>10 the genital powder use and as well as some of the data</p> <p>11 from the Nurses' Health Study, it is consistent that</p> <p>12 there -- the odds ratio is greater than 1.</p> <p>13 BY MR. JAMES:</p> <p>14 Q. So as long as the odds ratio, even if it's</p> <p>15 statistically insignificant, exceeds 1, then you are</p> <p>16 claiming that that's reflective of an association that</p> <p>17 is consistent with the case-control studies?</p> <p>18 MS. PARFITT: Objection. Form.</p> <p>19 THE WITNESS: I am saying that there is</p> <p>20 consistency in the direction of the effect.</p> <p>21 If I may clarify. If you look at something</p> <p>22 like alcohol use and ovarian cancer, which is a fact,</p> <p>23 which overall there seems to be little association</p> <p>24 between alcohol and ovarian cancer, if you look at the</p> <p>25 meta-analyses from there, the overall estimate is</p>	<p>1 significant, but I'm just saying that the direction of</p> <p>2 the effect is very consistent.</p> <p>3 Q. And we talked earlier today about the Berge</p> <p>4 paper; correct?</p> <p>5 A. Yes, we did.</p> <p>6 Q. And they have performed an analysis for</p> <p>7 heterogeneity on the -- by study design; right?</p> <p>8 A. If I could go back to that.</p> <p>9 Q. Sure.</p> <p>10 A. Okay.</p> <p>11 Q. Dr. Moorman, if we look at the abstract of</p> <p>12 the paper, at the beginning, this is the point we</p> <p>13 discussed earlier. Here, the authors say (as read):</p> <p>14 "The heterogeneity of results by</p> <p>15 study design detracts from a</p> <p>16 causal interpretation."</p> <p>17 Correct?</p> <p>18 A. That is the statement that they make in their</p> <p>19 abstract, yes.</p> <p>20 Q. Okay. And then we looked earlier also at the</p> <p>21 Figure 2; correct?</p> <p>22 A. Yes, we did.</p> <p>23 Q. Okay. And, again, that reflects an analysis</p> <p>24 of the cohorts as compared to the case-controls;</p> <p>25 correct?</p>

68 (Pages 266 to 269)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 270	Page 272
<p>1 A. Yes.</p> <p>2 Q. If you look at page 253 of the Berge article,</p> <p>3 and we look at the right column, the first -- the</p> <p>4 second full paragraph, the authors there state</p> <p>5 (as read):</p> <p>6 "The fact that the association</p> <p>7 between genital talc use and risk</p> <p>8 of ovarian cancer is present in</p> <p>9 case-control but not in cohort</p> <p>10 studies can be attributed to bias</p> <p>11 in the former type of studies."</p> <p>12 Do you see that?</p> <p>13 A. I do see what they say.</p> <p>14 I -- I think that they are not considering</p> <p>15 that there is also potential bias in the cohort</p> <p>16 studies. They say "bias in the former type of</p> <p>17 studies," not acknowledging the biases in the cohort</p> <p>18 studies.</p> <p>19 When you look at these data for the cohort</p> <p>20 studies, you look at the Gonzalez study, which again,</p> <p>21 I have referred to it as kind of an outlier with its</p> <p>22 relative risk of .73, there are many problems with</p> <p>23 that study. They assessed exposure in the past 12</p> <p>24 months. The level of exposure is very different than</p> <p>25 many of the other studies.</p>	<p>1 noted in some meta-analysis and</p> <p>2 reviews, there are considerations</p> <p>3 about those that should be taken</p> <p>4 into account."</p> <p>5 Q. Do you believe that there are inconsistencies</p> <p>6 in the literature with regard to dose-response? Yes</p> <p>7 or no.</p> <p>8 A. I think that, yes, that there -- that across</p> <p>9 the studies, some have found a dose-response, some</p> <p>10 have not.</p> <p>11 Q. At the bottom of page 30, you say that</p> <p>12 (as read):</p> <p>13 "When considering the studies that</p> <p>14 examine dose-response associations</p> <p>15 considering both dose and</p> <p>16 frequency to estimate the total</p> <p>17 number of applications of talc,</p> <p>18 the majority did find significant</p> <p>19 trends of higher risk with more</p> <p>20 lifetime applications of talc."</p> <p>21 Do you see that, where I read that?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. And so for that proposition, you're</p> <p>24 citing to eight studies. If you look at the</p> <p>25 footnotes, you would agree with me that that's</p>
Page 271	Page 273
<p>1 And so part of the heterogeneity by study</p> <p>2 design could be attributed to this Gonzalez study that</p> <p>3 has very significant biases.</p> <p>4 Q. If other experts for Plaintiffs in this MDL</p> <p>5 litigation have conceded that there is not consistency</p> <p>6 between the cohorts and the case-controls, then you</p> <p>7 would differ with those experts; correct?</p> <p>8 MS. PARFITT: Objection. Form.</p> <p>9 THE WITNESS: I have --</p> <p>10 MS. PARFITT: Misstates the evidence.</p> <p>11 Thank you.</p> <p>12 THE WITNESS: I have answered the</p> <p>13 question, I think I've answered it repeatedly, why</p> <p>14 I think that the aspect of consistency is met.</p> <p>15 BY MR. JAMES:</p> <p>16 Q. Okay. On dose-response -- on page 30, you</p> <p>17 include discussion of dose-response in the literature.</p> <p>18 A. Yes.</p> <p>19 Q. And you acknowledge in your report that there</p> <p>20 are inconsistencies in reported dose-response;</p> <p>21 correct?</p> <p>22 A. I -- what I state is (as read):</p> <p>23 "While the inconsistency in</p> <p>24 reported dose-response trends for</p> <p>25 talc and ovarian cancer have been</p>	<p>1 reflective of eight studies cited; correct?</p> <p>2 A. Yes.</p> <p>3 Q. And you're saying that five of the eight</p> <p>4 studies that have looked at dose and frequency</p> <p>5 together did find significant trends; correct?</p> <p>6 A. Yes.</p> <p>7 Q. Among those studies that you cite for that</p> <p>8 proposition that the majority of those studies reflect</p> <p>9 a dose-response, you cited to the Mills study;</p> <p>10 correct?</p> <p>11 A. I believe so.</p> <p>12 MS. PARFITT: And, Dr. Moorman, you</p> <p>13 have your binder in front of you as well if you need</p> <p>14 it.</p> <p>15 MR. JAMES: Okay. I'm going to mark</p> <p>16 Mills as Exhibit 30.</p> <p>17 (Exhibit No. 30 was marked for identification.)</p> <p>18 BY MR. JAMES:</p> <p>19 Q. I'm going to hand you two copies.</p> <p>20 And, again, this is one of the papers you've</p> <p>21 cited for the proposition that there's a dose-response</p> <p>22 in the majority of studies that have looked at</p> <p>23 frequency times duration; correct?</p> <p>24 A. Okay. Yes.</p> <p>25 Q. And we're looking at Table 2 as the relevant</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 274	Page 276
<p>1 table with the data; correct?</p> <p>2 A. Yes.</p> <p>3 Q. And if you look at Table 2, you go down to</p> <p>4 the cumulative use category, it says "frequency times</p> <p>5 duration"; correct?</p> <p>6 A. Yes.</p> <p>7 Q. And if I'm looking at this correctly,</p> <p>8 Dr. Moorman, doesn't the data in that table reflect an</p> <p>9 actual decrease in the odds ratio for the highest</p> <p>10 exposure category?</p> <p>11 MS. PARFITT: Objection. Form.</p> <p>12 THE WITNESS: It is -- the highest</p> <p>13 category, yes, does report an odds ratio of 1.06.</p> <p>14 BY MR. JAMES:</p> <p>15 Q. And based upon that, is it fair to say that</p> <p>16 this paper reflects a dose-response when measuring</p> <p>17 frequency times duration?</p> <p>18 A. They looked at the -- they did a test for</p> <p>19 trend, and we have a p-value of .051, so right at</p> <p>20 borderline statistically significant. Some people</p> <p>21 would argue that you should never use two decimal</p> <p>22 points for p-values. But nonetheless, it's -- the</p> <p>23 trend test was what I was referring to here, that it</p> <p>24 was right at borderline statistical significance.</p> <p>25 Q. And if you look at page 463 of the article,</p>	<p>1 Q. And they're not just acknowledging that</p> <p>2 there's not a perfect linear increase; they're saying</p> <p>3 that there's no dose-response for cumulative use.</p> <p>4 A. They say there is not a clear dose-response.</p> <p>5 I think -- you know, again, that's what they say. My</p> <p>6 conclusion here was, again, based on the test for</p> <p>7 trend that they did. I don't think that it was</p> <p>8 inaccurate, what I said here.</p> <p>9 Q. Another paper that you cite for the majority</p> <p>10 claim is the Terry 2013 paper; correct?</p> <p>11 A. Yes.</p> <p>12 Q. And do you know what the authors concluded in</p> <p>13 that paper about dose-response for cumulative use?</p> <p>14 A. May we look at that article?</p> <p>15 Q. Sure. It's Exhibit 24. And if we look at</p> <p>16 the abstract first together, the abstract says, the</p> <p>17 second sentence from the bottom (as read):</p> <p>18 "Among genital powder users, we</p> <p>19 observed no significant trend in</p> <p>20 risk with increasing number of</p> <p>21 lifetime applications assessed in</p> <p>22 quartiles."</p> <p>23 Did I read that correctly?</p> <p>24 MS. PARFITT: In the abstract?</p> <p>25 THE WITNESS: I'm sorry, I wasn't quite</p>
Page 275	Page 277
<p>1 the third full paragraph down -- 463 in the left</p> <p>2 column -- the authors -- this is in the authors'</p> <p>3 words. They say (as read):</p> <p>4 "As in other studies, the present</p> <p>5 study did not find a clear</p> <p>6 dose-response based on duration of</p> <p>7 use or cumulative use."</p> <p>8 Do you see that?</p> <p>9 A. Right. And they go on to say that -- again,</p> <p>10 I was basing what I said here based on their test for</p> <p>11 trend, and -- and I think they do acknowledge that in</p> <p>12 that category where they had relatively few exposed</p> <p>13 cases, they didn't -- it was not a perfectly linear</p> <p>14 association.</p> <p>15 Q. So the authors are concluding that there's</p> <p>16 not dose-response for cumulative use; correct?</p> <p>17 MS. PARFITT: Objection.</p> <p>18 BY MR. JAMES:</p> <p>19 Q. Yes or no? That's what the authors conclude</p> <p>20 in the text that we just read together?</p> <p>21 A. I -- what we read -- yes. I'm trying --</p> <p>22 let's see.</p> <p>23 Yeah, I think that they are acknowledging</p> <p>24 that it was not a perfect linear increase. My report</p> <p>25 was basing it on the test for trend that they did.</p>	<p>1 there with you. Could you --</p> <p>2 BY MR. JAMES:</p> <p>3 Q. Understood. No worries.</p> <p>4 A. Okay.</p> <p>5 Q. So second sentence from the bottom of the</p> <p>6 abstract, the author's conclusions on dose-response</p> <p>7 are as follows (as read):</p> <p>8 "Among genital powder users, we</p> <p>9 observed no significant trend in</p> <p>10 risk with increasing number of</p> <p>11 lifetime applications assessed in</p> <p>12 quartiles."</p> <p>13 A. That's what they describe, and --</p> <p>14 Q. I just asked, is that -- did I read that</p> <p>15 correctly?</p> <p>16 A. You did read that correctly.</p> <p>17 Q. So the authors of the paper that you've cited</p> <p>18 as one of the five papers that finds dose-response by</p> <p>19 measuring lifetime of cumulative use says the exact</p> <p>20 opposite; correct?</p> <p>21 MS. PARFITT: Objection.</p> <p>22 THE WITNESS: If I may take just a</p> <p>23 moment. I want to find the part of this paper that</p> <p>24 supported the statement that I made in my report.</p> <p>25 MR. JAMES: Sure. Let's go off the</p>

70 (Pages 274 to 277)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 278	Page 280
<p>1 record.</p> <p>2 THE VIDEOGRAPHER: Going off record at</p> <p>3 5:14 p.m.</p> <p>4 (Off the record.)</p> <p>5 THE VIDEOGRAPHER: Back on record at</p> <p>6 5:15 p.m.</p> <p>7 THE WITNESS: Okay. On page 817, it</p> <p>8 reads (as read):</p> <p>9 "Although a significant increase</p> <p>10 in risk with an increasing number</p> <p>11 of genital powder applications was</p> <p>12 found for non-mucinous epithelial</p> <p>13 ovarian cancer when non-users were</p> <p>14 included in the analysis."</p> <p>15 And it then goes on (as read):</p> <p>16 "Note trend in cumulative use was</p> <p>17 evident in analyses restricted to</p> <p>18 ever-users of genital powders."</p> <p>19 And so, again, my -- the statement that</p> <p>20 I had here, "a significant trend with increasing</p> <p>21 number of genital powder applications," they make the</p> <p>22 distinction of looking at the trend when you include</p> <p>23 non-users, and that's a pretty standard thing to do in</p> <p>24 epidemiology. It's -- you look -- can look as</p> <p>25 non-users as your reference group and then assess a</p>	<p>1 questions, Dr. Moorman.</p> <p>2 MR. JAMES: Michelle, is it fine if</p> <p>3 I have some time to review my notes while the others</p> <p>4 are asking questions and then come back?</p> <p>5 MS. PARFITT: Sure.</p> <p>6 MR. JAMES: Is that okay with you?</p> <p>7 MS. PARFITT: That's fine. Sure.</p> <p>8 MS. FOSTER: Can we go off and I'll</p> <p>9 switch.</p> <p>10 THE VIDEOGRAPHER: Going off the record</p> <p>11 at 5:18 p.m.</p> <p>12 (Off the record.)</p> <p>13 THE VIDEOGRAPHER: Back on record at</p> <p>14 5:20 p.m.</p> <p>15 CROSS-EXAMINATION BY COUNSEL FOR THE DEFENDANT</p> <p>16 IMERY'S TALC AMERICA, INC.</p> <p>17 BY MS. FOSTER:</p> <p>18 Q. Good evening, Dr. Moorman. We met a long</p> <p>19 time ago this morning. My name is Jennifer Foster.</p> <p>20 I represent one of the Defendants in this action,</p> <p>21 Imery's Talc America, Inc. Do you understand that?</p> <p>22 A. Yes, I do.</p> <p>23 Q. And before you got involved in this</p> <p>24 litigation, did you know who Imery's Talc America, Inc.</p> <p>25 was?</p>
Page 279	Page 281
<p>1 trend.</p> <p>2 I know what they say here, but I -- but</p> <p>3 I think that what I stated in my report is accurate,</p> <p>4 that they did find that a significant trend. So</p> <p>5 I don't think that I'm misstating what -- the data in</p> <p>6 the paper.</p> <p>7 BY MR. JAMES:</p> <p>8 Q. So the results that are reported by the</p> <p>9 authors in the abstract you disagree with; correct?</p> <p>10 MS. PARFITT: Objection. Form.</p> <p>11 BY MR. JAMES:</p> <p>12 Q. The statements in the abstract pertaining to</p> <p>13 dose-response, do you disagree with those statements?</p> <p>14 A. What they say is "among genital powder</p> <p>15 users." And so the statement that they make is</p> <p>16 accurate, but I think that they are citing data</p> <p>17 that -- it's one way to look at the data, but I think</p> <p>18 that considering the non-users in their test for trend</p> <p>19 is also a very well-accepted way to do that, to do a</p> <p>20 test for trend.</p> <p>21 And so I think that both -- they reported</p> <p>22 one aspect of their analysis, and I reported what</p> <p>23 I think accurately reflects another aspect of their</p> <p>24 analysis.</p> <p>25 Q. Okay. I am getting close to the end of my</p>	<p>1 A. No, I did not.</p> <p>2 Q. Had you ever heard of them before?</p> <p>3 A. No.</p> <p>4 Q. And do you have an understanding of who they</p> <p>5 are now that you've become involved in the litigation?</p> <p>6 A. I do.</p> <p>7 Q. And you understand that Imery's mines and</p> <p>8 supplies talc to Johnson & Johnson for use in some of</p> <p>9 its talcum powder products?</p> <p>10 A. That is my understanding, yes.</p> <p>11 Q. Do you understand that Imery's does not sell</p> <p>12 talcum powder products directly to consumers?</p> <p>13 A. That was my understanding, yes.</p> <p>14 Q. And based on some testimony earlier today</p> <p>15 about the basis of your opinions being grounded in</p> <p>16 epidemiology studies about talcum powder products, am</p> <p>17 I correct that you wouldn't have any personal</p> <p>18 knowledge with respect to the composition of the talc</p> <p>19 that Imery's mines and supplies to Johnson & Johnson?</p> <p>20 MS. PARFITT: Objection.</p> <p>21 THE WITNESS: No, I would not have that</p> <p>22 personal knowledge.</p> <p>23 BY MS. FOSTER:</p> <p>24 Q. And you have no opinions about any talc</p> <p>25 mining practices that Imery's employs; correct?</p>

71 (Pages 278 to 281)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 282	Page 284
<p>1 A. I know nothing about their mining practices.</p> <p>2 Q. And you have no opinions about Imerys's</p> <p>3 compliance with any applicable standards or</p> <p>4 specifications regarding the mining of talc; correct?</p> <p>5 A. I do not know anything about that.</p> <p>6 Q. And I'm going to be hopping around a lot</p> <p>7 because Mr. James covered a lot of ground, so just</p> <p>8 bear with me. If I go somewhere and you don't know</p> <p>9 what I'm talking about, please just tell me you don't</p> <p>10 know what I'm talking about --</p> <p>11 A. Okay.</p> <p>12 Q. -- and I'll rephrase so that we can get on</p> <p>13 the same page.</p> <p>14 One of the first things you talked about</p> <p>15 this morning when you were talking to Mr. James is</p> <p>16 that you have entered a period I think you called</p> <p>17 preretirement transition. Do I have that right?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. And do you have a retirement date in</p> <p>20 mind?</p> <p>21 A. That's still somewhat being discussed with my</p> <p>22 husband.</p> <p>23 Q. Okay. So you don't have a set "I'm going to</p> <p>24 retire in a year," for example?</p> <p>25 A. The exact date is not defined yet.</p>	<p>1 A. Yes, that is.</p> <p>2 Q. And is that a study that's designed to</p> <p>3 collect new data from study participants, or is that</p> <p>4 going to be an evaluation of data that you already</p> <p>5 have collected from other studies?</p> <p>6 A. It is a consortium that is planning to</p> <p>7 analyze data that have already been collected. It</p> <p>8 involves -- I believe it is a total of seven studies;</p> <p>9 some case-control, some cohort studies.</p> <p>10 Q. And -- were you finished? I'm sorry.</p> <p>11 A. Go ahead.</p> <p>12 Q. And how were the studies selected to be</p> <p>13 included in that consortium?</p> <p>14 A. It was -- the purpose of that was to try to</p> <p>15 put more data together, especially related to women of</p> <p>16 African ancestry. So they're all US studies, so</p> <p>17 African American. Recognizing that the AACES study,</p> <p>18 with about 600 cases, we still have some issues with</p> <p>19 statistical power. So we contacted -- Dr. Schildkraut</p> <p>20 is the PI on this study as well.</p> <p>21 And so studies that had a reasonable number</p> <p>22 of African American study participants, they were</p> <p>23 contacted to see if they were interested in</p> <p>24 participating in such a study.</p> <p>25 And so it includes studies such as the Black</p>
Page 283	Page 285
<p>1 Q. And when you do retire, are you still going</p> <p>2 to have any involvement with what you've defined as</p> <p>3 the AACES study, the African American Cancer</p> <p>4 Epidemiology Study?</p> <p>5 A. That is still to be determined as well.</p> <p>6 Q. And am I correct that that study is still</p> <p>7 ongoing?</p> <p>8 A. The funding for that study ended -- I think</p> <p>9 it was 2015/2016. I don't recall the exact date. And</p> <p>10 so we have not collected any data for that study since</p> <p>11 that time.</p> <p>12 We have continued to do analysis of data</p> <p>13 that we have collected, and we are also trying to</p> <p>14 secure funding to continue data collection with that</p> <p>15 study.</p> <p>16 Q. That was going to be my question. Who have</p> <p>17 you made that request to for additional funding?</p> <p>18 A. The grant application was submitted to</p> <p>19 National Cancer Institute.</p> <p>20 Q. And that's who funded the original research;</p> <p>21 correct?</p> <p>22 A. That is correct.</p> <p>23 Q. And you also mentioned a publication that is</p> <p>24 in draft form regarding something called the OCWAA</p> <p>25 Consortium; is that correct?</p>	<p>1 Women's Health Study Cohort, that's out of Boston</p> <p>2 University; the Multiethnic Cohort, which is out of</p> <p>3 California; the Southern Community Cohort Study; the</p> <p>4 Women's Health Initiative; as well as a Los Angeles</p> <p>5 case-control study and a case-control study out of</p> <p>6 Chicago, in addition to the AACES study.</p> <p>7 I think that that's most of them.</p> <p>8 Q. Okay. Are you involved in any current</p> <p>9 research where the intent is to collect new data for</p> <p>10 evaluation of risk factors for ovarian cancer?</p> <p>11 A. Other than what I described to you, that we</p> <p>12 hope to -- that we are applying for funding to</p> <p>13 continue the AACES study, I'm not currently doing any</p> <p>14 data collection related to ovarian cancers.</p> <p>15 Q. Are the coauthors and coinvestigators that</p> <p>16 you worked with on the AACES and the North Carolina</p> <p>17 Ovarian Cancer Study aware of your involvement in the</p> <p>18 talcum powder litigation?</p> <p>19 A. Some of them are. I -- you know, as --</p> <p>20 I have disclosed it on one publication, and if they've</p> <p>21 read it, they are aware. I've discussed it with some</p> <p>22 of them but not all of them. You know, I haven't had</p> <p>23 a conversation, per se, with all of them.</p> <p>24 Q. And you mentioned earlier, with respect to</p> <p>25 some of the new publications that are in draft form</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 286</p> <p>1 that are currently in the peer review process, that</p> <p>2 they have talc as a -- as a confounding factor under</p> <p>3 investigation; correct?</p> <p>4 A. I think -- I'm going to reread your --</p> <p>5 Q. I can rephrase it.</p> <p>6 I think when you were talking earlier about</p> <p>7 the studies that you have in draft, the question was</p> <p>8 whether or not you had any publications that, you</p> <p>9 know, mentioned talc. And I thought your testimony</p> <p>10 was that talc was listed as a possible confounding</p> <p>11 factor in some of the studies that were in draft form.</p> <p>12 Is that correct?</p> <p>13 A. Right. I mentioned that specifically in</p> <p>14 relation to the infertility and ovarian cancer paper</p> <p>15 that is in draft form, it's -- talc is considered as a</p> <p>16 confounder there.</p> <p>17 In regard to the description of the OCWAA</p> <p>18 study, that paper, we are listing it as one of the</p> <p>19 factors that we are likely to evaluate as a risk</p> <p>20 factor for ovarian cancer.</p> <p>21 Q. Okay. And my question is have you ever</p> <p>22 included asbestos as a risk factor under investigation</p> <p>23 in your epidemiology studies?</p> <p>24 A. If I am not mistaken, I think that we had a</p> <p>25 question on the AACES questionnaire that we asked if</p>	<p style="text-align: right;">Page 288</p> <p>1 did you have a particular paper in -- in mind?</p> <p>2 BY MS. FOSTER:</p> <p>3 Q. Not with 20 minutes left, no.</p> <p>4 A. I'm sorry. I just -- you know, you're asking</p> <p>5 me what did they mean, and I'm not even sure which</p> <p>6 paper might have described something as a weak</p> <p>7 positive association, and I'm not sure who would have</p> <p>8 used that terminology or what was going through their</p> <p>9 mind when they chose those words.</p> <p>10 Q. I assume there are standard epidemiology</p> <p>11 textbooks that you use in your field; correct?</p> <p>12 A. Yes.</p> <p>13 Q. Okay. And what are some of your go-to</p> <p>14 epidemiology textbooks?</p> <p>15 A. Let's see. Ken Rothman's Modern Epidemiology</p> <p>16 is -- different editions of it have been around since</p> <p>17 I was in school 30 years ago. I still refer to that.</p> <p>18 When I have taught the physician assistant</p> <p>19 students, the textbook that we use, which is a little</p> <p>20 bit lower-level textbook, was going to us. Those are</p> <p>21 probably my go-to ones.</p> <p>22 Q. Okay. Do any of the standard epidemiology</p> <p>23 textbooks use terms like "weak," "modest," "strong,"</p> <p>24 to describe associations?</p> <p>25 A. I -- I imagine that in the textbooks, they</p>
<p style="text-align: right;">Page 287</p> <p>1 women had ever been -- ever had a job where they were</p> <p>2 exposed to asbestos, and I don't know that we have</p> <p>3 analyzed that data yet.</p> <p>4 Q. Okay. And you had some discussion with</p> <p>5 Mr. James earlier today about different types of</p> <p>6 terminology that might be used to describe</p> <p>7 associations in the epidemiology literature.</p> <p>8 Do you recall that?</p> <p>9 A. Yes.</p> <p>10 Q. And you were talking about weak associations,</p> <p>11 modest associations, strong associations. Do you</p> <p>12 remember that general discussion?</p> <p>13 A. Yes.</p> <p>14 Q. Now, as an epidemiologist, how would you</p> <p>15 define a weak positive association?</p> <p>16 A. As we have said before, there is no absolute</p> <p>17 cut-point what's a weak association, what's a modest,</p> <p>18 what's a moderate association. I -- I can't put a</p> <p>19 number on that. I don't think any epidemiologist</p> <p>20 could.</p> <p>21 Q. In papers that you've authored that have used</p> <p>22 the words "weak positive association," what do the</p> <p>23 authors mean by that?</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25 THE WITNESS: I'm -- I'm not -- if --</p>	<p style="text-align: right;">Page 289</p> <p>1 might use that. But the point that I have been trying</p> <p>2 to make is that there is no numerical value to go</p> <p>3 along with those descriptors.</p> <p>4 Q. All right. Switching topics, I want to talk</p> <p>5 a little bit about some of the things that you</p> <p>6 reviewed before you came and gave your deposition</p> <p>7 today.</p> <p>8 Now, you confirmed earlier that you reviewed</p> <p>9 the reports of some of the other Plaintiffs' experts</p> <p>10 in this case; correct?</p> <p>11 A. Yes.</p> <p>12 Q. And you reviewed those all between the time</p> <p>13 that you finished your report and when you came here</p> <p>14 to testify; correct?</p> <p>15 A. That is correct.</p> <p>16 Q. And those were all provided to you by</p> <p>17 Plaintiffs' counsel; correct?</p> <p>18 A. That is correct.</p> <p>19 Q. And how did you choose which of the 22 expert</p> <p>20 reports that you were going to sit down and read?</p> <p>21 A. I knew which of the ones that were more of</p> <p>22 the epidemiology-focused ones. And because that is my</p> <p>23 area of expertise, those were the ones that I went to</p> <p>24 first.</p> <p>25 Also, some of it was, you know, some of the</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 290	Page 292
<p>1 names that I recognized: David Kessler, former chair 2 of the -- former head of the FDA; Daniel 3 Clarke-Pearson, who is a gynecologic oncologist who 4 was formerly at Duke. He's now at UNC. 5 Q. Do you know Dr. Clarke-Pearson? 6 A. Only by reputation. 7 Q. You haven't talked to him about your opinions 8 in this litigation? 9 A. No, I have not. 10 Q. And you haven't talked to any other 11 Plaintiffs' expert about your opinions in this 12 litigation? 13 A. No, I have not. 14 Q. In reviewing those reports, did you work 15 under the assumption that the authors of those reports 16 had employed generally accepted methodologies in 17 forming their conclusions? 18 A. I -- I assumed that they had. You know, some 19 of the experts, they are names that I know, even if 20 I don't know the individual personally. You knows, 21 Dr. Siemiatycki, Dr. McTiernan, these are very 22 well-known epidemiologists. And so my assumption is 23 that they use generally accepted methodologies. 24 Q. I noticed on the 25 additional-materials-provided list -- I think it was</p>	<p>1 2016, and then updated it to make sure that my report 2 reflected the current literature. 3 Q. Did you do any kind of Bradford Hill analysis 4 of the claimed association between talcum powder usage 5 and ovarian cancer before you were retained as an 6 expert in the talcum powder litigation? 7 A. Doing -- considering the talcum powder -- or 8 considering the Bradford Hill criteria, this is 9 something that we do in our work all the time. It's 10 probably not as formalized as what was done here. 11 As you're aware, I was a coauthor, but I was 12 not the lead author on the AACES study of talc and 13 ovarian cancer. And in regard to the North Carolina 14 Ovarian Cancer Study, that was not the major focus of 15 the -- those papers that reported on talc and -- that 16 reported on talc as a risk factor. 17 So have I done the Bradford Hill criteria? 18 Certainly not in the detail that I have done for the 19 report that I prepared. 20 Q. And when you were -- when Mr. James asked you 21 about the NCI PDQ -- and you all looked at that as an 22 exhibit to the deposition. 23 Do you recall that earlier today? 24 A. Yes, I do. 25 Q. And one of the things that you mentioned is</p>
Page 291	Page 293
<p>1 marked as Exhibit 8 earlier. It's a document that 2 I believe you said counsel had prepared, and it has 3 the expert reports on it. It also has a couple of 4 deposition transcripts on it from Dr. Plunkett and 5 Dr. Singh. 6 Did you review either of those before you 7 came and testified today? 8 A. Dr. Plunkett and Dr. Singh, S-I-N-G-H? 9 Q. Yes. 10 A. I don't believe that I read Dr. Plunkett's 11 deposition. I did read a fair bit of Dr. Singh's 12 deposition. 13 Q. When did you do that? 14 A. Probably a week or so ago. 15 Q. Do you have any intention of reading the rest 16 of the reports that Plaintiffs' counsel sent to you 17 after you're closed here today? 18 A. I think that it is possible that I will read 19 some of them, time permitting. 20 Q. You testified about a literature search that 21 you conducted on talcum powder and ovarian cancer. 22 When did you first conduct that search? 23 A. I believe that probably the first time I did 24 that search was not long after I was contacted about 25 possible involvement in this. So probably summer of</p>	<p>1 you see some kind of inconsistency in the way that NCI 2 evaluates data as to whether there is adequate 3 evidence of association or inadequate evidence of 4 association and specifically used the example of the 5 way that that they evaluated the breastfeeding data. 6 Do you remember that? 7 A. Right. What I -- I think the point that 8 I was trying to make when I was asked about that is 9 that the NCI PDQ, they do not describe their 10 methodology. So we're kind of left at what method did 11 they use to evaluate the data? Did they do a complete 12 systematic review, or was it -- was it something less 13 than a complete systematic review? 14 And my point is that, from the information 15 provided, we don't know what methods they used. 16 Q. Have you ever tried to communicate with any 17 of the editorial board members who write the NCI PDQ? 18 A. No, I have not. 19 Q. And you haven't submitted your report to 20 IARC; correct? 21 A. My -- 22 Q. Your expert report. You haven't submitted a 23 copy of your expert report to IARC for their 24 consideration; correct? 25 A. No, I have not.</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 294	Page 296
<p>1 Q. Being conscious of the fact that we have</p> <p>2 limited time left, I'm going to -- okay. One last</p> <p>3 question.</p> <p>4 In terms of the expert report that you</p> <p>5 provided in the MDL litigation that we've been talking</p> <p>6 about all day today, are all of the opinions that you</p> <p>7 intend to give in this litigation contained within</p> <p>8 that report?</p> <p>9 A. I believe they are, yes.</p> <p>10 MS. FOSTER: I don't have anything else</p> <p>11 for you. So I'm going to pass you on to my colleague</p> <p>12 here. Thank you very much.</p> <p>13 THE WITNESS: Okay.</p> <p>14 CROSS-EXAMINATION BY COUNSEL FOR THE DEFENDANTS</p> <p>15 PERSONAL CARE PRODUCTS COUNCIL</p> <p>16 BY MS. APPEL:</p> <p>17 Q. Hi, Dr. Moorman. You can you hear me okay?</p> <p>18 A. I can, yes.</p> <p>19 Q. And just as a reminder from this morning,</p> <p>20 I am Renée Appel, and I represent Personal Care</p> <p>21 Products Council. And I just have a handful of</p> <p>22 questions to follow up on.</p> <p>23 When did you first form your opinion in your</p> <p>24 expert report that talcum powder products can cause</p> <p>25 ovarian cancer?</p>	<p>1 referring to talcum powder products?</p> <p>2 A. Yes, because all of the literature is -- the</p> <p>3 epidemiologic literature is based on talcum powder</p> <p>4 products, whatever the women reported that they used.</p> <p>5 Q. So is it correct, Dr. Moorman, that you had</p> <p>6 not formed an opinion as to whether pure talc is a</p> <p>7 risk factor for forming ovarian cancer?</p> <p>8 MS. PARFITT: Objection.</p> <p>9 THE WITNESS: Again, my opinion is</p> <p>10 based on the product that women have used, and my</p> <p>11 understanding is that all of the products, they have</p> <p>12 other constituents in them. So they may contain, you</p> <p>13 know, as we have discussed previously, fragrances, for</p> <p>14 example. We have also talked about that there are</p> <p>15 other -- there's evidence to suggest other</p> <p>16 constituents, such as asbestos or possibly heavy</p> <p>17 metals.</p> <p>18 BY MS. APPEL:</p> <p>19 Q. And as to those constituents, would you defer</p> <p>20 to other experts to opine on them, based on the</p> <p>21 examples you just provided, fragrances or heavy</p> <p>22 metals?</p> <p>23 MS. PARFITT: Objection. Form.</p> <p>24 THE WITNESS: You're asking me defer to</p> <p>25 other estimates to opine on them in what sense? Opine</p>
Page 295	Page 297
<p>1 A. I think that we have talked about this, that</p> <p>2 the literature on talc and ovarian cancer has been</p> <p>3 accruing since 1982, and to say at what point I formed</p> <p>4 my opinion that it causes ovarian cancer, I can't</p> <p>5 pinpoint that date.</p> <p>6 I can say that I have considered talc as a</p> <p>7 risk factor for ovarian cancer for quite some time.</p> <p>8 Just over my career, it just seems like it has been an</p> <p>9 accumulating volume of evidence.</p> <p>10 Q. Did you hold that opinion before you were</p> <p>11 retained as an expert in the talc litigation dating</p> <p>12 back to the Ingham case?</p> <p>13 A. I think that, yes, I did.</p> <p>14 Q. But, sitting here today, you can't recall a</p> <p>15 specific year or point in time in which you formed</p> <p>16 that opinion?</p> <p>17 MS. PARFITT: Objection.</p> <p>18 THE WITNESS: I think that I've</p> <p>19 answered that. I can't pinpoint at what point that</p> <p>20 I concluded it was a risk factor for ovarian cancer.</p> <p>21 It's been something that I've considered a risk factor</p> <p>22 for ovarian cancer for quite -- quite a number of</p> <p>23 years.</p> <p>24 BY MS. APPEL:</p> <p>25 Q. And when you refer to "it," Doctor, are you</p>	<p>1 on them in what sense?</p> <p>2 BY MS. APPEL:</p> <p>3 Q. Sure. Would you defer to other experts to</p> <p>4 opine on whether those particular constituents in</p> <p>5 isolation are a risk factor for ovarian cancer?</p> <p>6 MS. PARFITT: Objection. Form. Asked</p> <p>7 and answered.</p> <p>8 THE WITNESS: Okay. Those particular</p> <p>9 constituents in isolation are a risk factor for</p> <p>10 ovarian cancer.</p> <p>11 I think that we have discussed this</p> <p>12 previously today, that what is the evidence about, for</p> <p>13 example, the heavy metals in isolation in ovarian</p> <p>14 cancer and limited to -- limited epidemiologic data in</p> <p>15 that regard.</p> <p>16 So I don't know that I'm deferring to other</p> <p>17 experts, but, as I phrased it earlier today, I --</p> <p>18 the -- whether or not these substances are in talc</p> <p>19 products, it adds to the biologic plausibility, but</p> <p>20 the epidemiologic data is based on the talc products.</p> <p>21 That's what the women were exposed to.</p> <p>22 BY MS. APPEL:</p> <p>23 Q. Okay. So in forming your opinion, you are</p> <p>24 assuming that those constituents that you've</p> <p>25 mentioned -- heavy metals, asbestos -- that they are</p>

75 (Pages 294 to 297)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 298	Page 300
<p>1 in the talc powder product that you've rendered an 2 opinion about today? 3 MS. PARFITT: Objection. Misstates her 4 earlier opinions. 5 You might want to read that. 6 THE WITNESS: I -- I am not making, 7 really, any assumptions that these are in the 8 products. My -- you know, my focus on the 9 epidemiologic data is based on the use of the talc 10 products, whatever is contained in them. 11 BY MS. APPEL: 12 Q. In your report on page 30, you've indicated 13 that -- second paragraph, I'm reading from. And I'll 14 give you a moment to turn to it. (As read): 15 "For an association like talc and 16 ovarian cancer, the dose that is 17 most relevant is the amount of 18 talc that actually reaches the 19 fallopian tubes and ovaries." 20 Did I read that correctly? 21 A. Yes, you did. 22 Q. There is, in fact, though, no dose that has 23 been determined that actually reaches the fallopian 24 tubes and the ovaries in any of the studies that 25 you've relied upon; correct?</p>	<p>1 MS. PARFITT: Objection. Form. 2 THE WITNESS: I think that the sentence 3 that followed the one that you're reading is that, for 4 all the pragmatic reasons, we rely on the measures of 5 external application as a surrogate of the level of 6 exposure. There's no way that we could measure what 7 dose of talc reached the ovaries or the fallopian 8 tubes for something that women might have applied over 9 20, 30, 40 years of their lives. 10 BY MS. APPEL: 11 Q. Earlier today, you had discussed the 12 hierarchy of scientific evidence. 13 Do you recall that discussion? 14 A. I don't think that I used that terminology, 15 but I think that -- in talking about the 16 meta-analyses, yes. Yes. 17 Q. In terms of that hierarchy, that you 18 understand that I'm referring to based on that prior 19 discussion, where do cohort studies fall in comparison 20 to case-control studies? 21 MS. PARFITT: Objection. Asked and 22 answered. 23 THE WITNESS: Okay. If you have a 24 cohort study that was able to determine exposure 25 completely and accurately, and follow women for a</p>
Page 299	Page 301
<p>1 MS. PARFITT: Objection. Form. 2 THE WITNESS: Let's see. 3 BY MS. APPEL: 4 Q. I can rephrase if you don't understand. 5 A. If you wouldn't mind, please. 6 Q. Absolutely. 7 In the studies that you've relied upon in 8 forming your opinion, none of those studies have 9 determined a particular dose of talc that actually 10 reaches the fallopian tubes and ovaries; correct? 11 MS. PARFITT: Objection. 12 THE WITNESS: Okay. So if we are 13 talking about the epidemiologic studies, there -- no, 14 of course, they did not measure what dose of talc 15 reached the ovaries and fallopian tubes. That would 16 not be feasible to do for -- reflecting the many, many 17 years of use, and also it would be completely 18 unfeasible to do something like that in an 19 epidemiologic study. 20 BY MS. APPEL: 21 Q. But you maintain the opinion that a 22 determination of that amount -- the amount being what 23 talc reaches the fallopian tubes and ovaries -- is 24 important to making a determination about an 25 association between talc and ovarian cancer; correct?</p>	<p>1 sufficient period of time, I think most people would 2 consider that a -- generally a stronger design than a 3 case-control study. 4 But, as I have indicated in my report, you 5 can't rely just on what is the stronger study design, 6 in general. You look -- have to look at the strengths 7 and limitations of the individual studies. 8 Cohort studies have some strengths; they 9 have some notable weaknesses. And I've described 10 those weaknesses several times over the course of 11 today. And I also acknowledge that case-control 12 studies have some weaknesses, but they also have 13 noticeable strengths too. 14 BY MS. APPEL: 15 Q. Is it accurate, Dr. Moorman, that, when you 16 were previously discussing meta-analyses and where 17 that falls on the hierarchy, you were envisioning a 18 pyramid graphic? Is that correct? 19 A. I have -- yes, I have seen graphics that 20 depict it like that. 21 Q. And in those particular graphics, where is 22 cohort studies listed in comparison to case-control 23 studies? 24 MS. PARFITT: Objection. 25 THE WITNESS: As I have said, that in</p>

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 302	Page 304
<p>1 that pyramid, it is -- typically, the cohort study is</p> <p>2 ranked as a stronger study design. But, again, I</p> <p>3 cannot emphasize strongly enough that you have to</p> <p>4 consider strengths and weaknesses of individual.</p> <p>5 BY MS. APPEL:</p> <p>6 Q. And, Dr. Moorman, have you considered</p> <p>7 publishing your expert report or the findings that you</p> <p>8 arrived at in your expert report?</p> <p>9 A. I have considered it. I have not actually</p> <p>10 done anything to translate it into a manuscript.</p> <p>11 MS. APPEL: Okay. Thank you,</p> <p>12 Dr. Moorman. That concludes my questions.</p> <p>13 THE WITNESS: Okay.</p> <p>14 MR. JAMES: I think there's about eight</p> <p>15 minutes. Off the record.</p> <p>16 THE VIDEOGRAPHER: Going off the record</p> <p>17 at 5:50 p.m.</p> <p>18 (Discussion off the record.)</p> <p>19 THE VIDEOGRAPHER: Back on record at</p> <p>20 5:51 p.m.</p> <p>21 FURTHER EXAMINATION BY COUNSEL FOR THE</p> <p>22 JOHNSON & JOHNSON DEFENDANTS</p> <p>23 BY MR. JAMES:</p> <p>24 Q. Dr. Moorman, in regard to your general cause</p> <p>25 opinion, do you hold the opinion that the evidence is</p>	<p>1 is sufficient to conclude that inhaled talcum powder</p> <p>2 can cause ovarian cancer?</p> <p>3 A. I do not think that there are epidemiologic</p> <p>4 studies that have actually looked at inhaled talcum</p> <p>5 powder in relation to ovarian cancer.</p> <p>6 Q. And so is your answer that -- let me just ask</p> <p>7 this again.</p> <p>8 Do you believe there's sufficient evidence</p> <p>9 upon which you can conclude that inhaled talc powder</p> <p>10 causes ovarian cancer?</p> <p>11 MS. PARFITT: Objection.</p> <p>12 THE WITNESS: I think that I answered</p> <p>13 that when I said that I don't think that there are</p> <p>14 epidemiologic studies that have looked at that. So</p> <p>15 I can't say that there is sufficient evidence.</p> <p>16 BY MR. JAMES:</p> <p>17 Q. Dr. Moorman, are you generally aware that, in</p> <p>18 the African-American population, there is a lower</p> <p>19 incidence of ovarian cancer?</p> <p>20 A. Yes.</p> <p>21 Q. And you have -- have you also seen in the</p> <p>22 literature that there is at least some discussion in</p> <p>23 the literature that the prevalence of talcum powder</p> <p>24 used in the African-American populations may be</p> <p>25 higher?</p>
Page 303	Page 305
<p>1 sufficient to support a general cause opinion for all</p> <p>2 subtypes of ovarian cancer or do you distinguish among</p> <p>3 the subtypes?</p> <p>4 A. Okay. The majority of the studies looked at</p> <p>5 epithelial ovarian cancer as a whole. Some of the</p> <p>6 studies did look at subtypes. As we are aware, the</p> <p>7 serous subtype is the vast majority, probably about</p> <p>8 60 -- maybe "vast majority" is overstating it. But</p> <p>9 serous subtypes are roughly 60 percent of ovarian</p> <p>10 cancer cases. And so the studies that looked at the</p> <p>11 subtypes tended to focus on that.</p> <p>12 The other subtypes -- the mucinous, the</p> <p>13 clear cell, and the other subtypes -- they are a much</p> <p>14 smaller percentage of epithelial ovarian cancer. And</p> <p>15 so there's really not adequate data to make a</p> <p>16 conclusion about these subtypes.</p> <p>17 Q. With regard to inhalation, which you touch</p> <p>18 upon in your report, do you hold the opinion that</p> <p>19 inhalation of talcum powder products can cause ovarian</p> <p>20 cancer?</p> <p>21 A. I have stated that that is a possible route</p> <p>22 of exposure to the ovaries. The epidemiologic studies</p> <p>23 have not specifically addressed the risk associated</p> <p>24 with inhalation only of talcum powder products.</p> <p>25 Q. So is there evidence upon which you believe</p>	<p>1 A. Yes.</p> <p>2 Q. If both of those things are true, can you</p> <p>3 provide us an explanation as to why -- why that would</p> <p>4 be the case?</p> <p>5 A. There are many causes of ovarian cancer. And</p> <p>6 some of the risk factors are more common in</p> <p>7 African-American women; some are less common.</p> <p>8 So when you consider the whole spectrum of</p> <p>9 risk factors, you know, breastfeeding, pregnancy, oral</p> <p>10 contraceptive use, to pinpoint one factor like talc</p> <p>11 that is used more frequently in African Americans and</p> <p>12 then say that that conflicts with the lower incidence</p> <p>13 of ovarian cancer that we see in African-American</p> <p>14 women, it doesn't take into account the full spectrum</p> <p>15 of risk factors.</p> <p>16 Q. With regard to the Health Canada assessment</p> <p>17 that we discussed much earlier today, do you</p> <p>18 understand that that assessment is in draft form</p> <p>19 currently?</p> <p>20 MS. PARFITT: Objection.</p> <p>21 THE WITNESS: My understanding is that</p> <p>22 the scientific assessment they did is complete and</p> <p>23 that they are -- that there is a period of comment</p> <p>24 that -- so, I'm sorry, I want to make sure...</p> <p>25</p>

77 (Pages 302 to 305)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 306	Page 308
<p>1 BY MR. JAMES: 2 Q. Do you understand that right now that 3 assessment is currently in the process of a comment 4 period? 5 MS. PARFITT: Objection. Form. 6 THE WITNESS: My understanding is the 7 assessment of the risk that they did, that is 8 complete, and then they are assessing -- or it is in a 9 comment period. And I think that, you know, 10 potentially, if there were some serious concerns 11 raised, they might revisit the risk assessment that 12 they did. But my understanding is what they published 13 is their -- that they felt like the risk assessment 14 was complete. 15 BY MR. JAMES: 16 Q. And to be very quick here, I understand that 17 one of the materials provided to you in the additional 18 materials list was the Taher paper; correct? 19 A. Yes. 20 Q. And do you understand that the Taher paper is 21 one of the items discussed in the Health Canada 22 assessment? 23 A. Yes. 24 Q. And do you understand the Taher paper's 25 conclusion is consistent with the IARC's conclusion of</p>	<p>1 A. Yes, I -- 2 MS. PARFITT: Is the question is that 3 what it says? 4 BY MR. JAMES: 5 Q. That is the question. 6 We had a discussion earlier today about 7 possible cause; correct? 8 A. Yes. 9 MS. PARFITT: Objection. 10 BY MR. JAMES: 11 Q. And, Dr. Moorman, with respect to the 12 Bradford Hill analysis -- 13 MS. PARFITT: Can we stop for a minute? 14 Are you going to tell us when we're off and 15 when we're done? 16 THE VIDEOGRAPHER: Just one minute. 17 MS. PARFITT: Thank you. Oh, that's 18 good. 19 BY MR. JAMES: 20 Q. With respect to your Bradford Hill 21 analysis -- and this should be my last question -- 22 A. Okay. 23 Q. -- you will agree with me that in order to 24 reach a causal conclusion, you must rely on items 25 other than the cohorts, case controls, and</p>
Page 307	Page 309
<p>1 possible cause? 2 MS. PARFITT: Objection. Form. 3 Misstates the evidence. 4 THE WITNESS: If you have the Taher 5 paper -- again, just recalling exactly what they 6 stated, I -- too many papers to remember all the 7 detail. 8 BY MR. JAMES: 9 Q. When is the last time you reviewed the Taher 10 paper? 11 A. I would say probably a week or two ago. 12 MR. JAMES: So if Michelle doesn't cut 13 me off, I will hand you a copy of it. I'm going to 14 mark it as Exhibit 31. 15 (Exhibit No. 31 was marked for identification.) 16 BY MR. JAMES: 17 Q. I'll hand you two copies. 18 Okay. And, Dr. Moorman, again, because I'm 19 running out of time, I'll direct you to the precise 20 portion of the article that founds my question. It's 21 on page 49, and it's in the conclusion section of the 22 paper. 23 And you see in the last sentence -- in the 24 last sentence, they report that the data indicates 25 "possible cause of ovarian cancer"?</p>	<p>1 meta-analyses of the epidemiologic literature; 2 correct? 3 MS. PARFITT: Objection. Form. 4 THE WITNESS: The -- some of the 5 Bradford Hill aspects which I think I discussed in my 6 report were the biological plausibility, and so I did 7 rely on literature other than the epidemiologic 8 literature. 9 BY MR. JAMES: 10 Q. And those are necessary as part of your 11 methodology to reach a causal conclusion; correct? 12 MS. PARFITT: Objection. Form. 13 THE WITNESS: They are a consideration. 14 When you do a Bradford Hill analysis, of course you 15 take into account the biological plausibility and the 16 data that may come from cancer biology studies, animal 17 studies, and so on. So yes, it should be considered. 18 MR. JAMES: Okay. Dr. Moorman, thank 19 you for your time. 20 THE WITNESS: Okay. 21 MS. PARFITT: Can we go off the record, 22 please. 23 THE VIDEOGRAPHER: Going off the record 24 at 6:01 p.m. 25 (Recess taken from 6:01 p.m. to 6:14 p.m.)</p>

78 (Pages 306 to 309)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 310	Page 312
<p>1 THE VIDEOGRAPHER: Back on record at 2 6:15 p.m. 3 CROSS-EXAMINATION BY COUNSEL FOR THE PLAINTIFF 4 BY MS. PARFITT: 5 Q. Dr. Moorman, good evening. 6 A. Good evening. 7 Q. I just have a few questions to follow up with 8 counsel for J&J and then for PCPC. 9 Dr. Moorman, you were asked not too long ago 10 by Mr. James a question with regard to your general 11 causation opinions as they relate to does talc -- do 12 talcum powder products cause ovarian cancer. 13 Do you remember that discussion? 14 A. Yes, I do. 15 Q. All right. And I believe the question dealt 16 with subtypes of epithelial ovarian cancer. 17 Do you remember that? 18 A. Yes. 19 Q. All right. And I believe your testimony was 20 that there's really not adequate data to make a 21 conclusion about the subtypes. 22 Did you mean, when you said that, that 23 there's not adequate data to make a conclusion about 24 these other subtypes, that that was because the 25 non-serous subtypes were relatively rare?</p>	<p>1 of the opinion of Health Canada vis-à-vis exposure to 2 talcum powder products and ovarian cancer? 3 A. My -- my understanding is that Health Canada 4 indicated that talcum powder products can cause 5 ovarian cancer. 6 Q. Mr. James showed you a study, the Taher 7 study. 8 A. Yes. 9 Q. And you had an opportunity to review the 10 Taher study as well; correct? 11 A. Yes. 12 Q. Is the Taher study a -- one of the pieces of 13 evidence that you looked at in your review of the 14 Health Canada assessment? 15 A. One of -- it's one of the pieces of evidence, 16 but not the sole body of evidence that they 17 considered. 18 Q. Okay. And is the Taher study also considered 19 a meta-analysis? 20 A. Yes. 21 Q. Okay. For purposes of rendering your 22 opinions in this case, that talcum powder products can 23 cause ovarian cancer, you have shared with the ladies 24 and gentlemen of the jury that you have reviewed 25 multiple meta-analyses; correct?</p>
Page 311	Page 313
<p>1 A. Yes, but the bulk of the literature is 2 addressing epithelial ovarian cancer, which includes 3 all of the subtypes. 4 Q. All right. So that the ladies and gentlemen 5 are clear as to what your opinion is, is it your 6 opinion that talcum powder products can cause -- or 7 exposure -- let me strike that. 8 Is it your opinion that exposure to talcum 9 powder products can cause ovarian cancer? Is that 10 your opinion? 11 A. That is my opinion. 12 Q. All right. And does that include all types 13 of epithelial ovarian cancer? 14 A. That -- yes. The data are based -- are 15 largely based on all types of epithelial ovarian 16 cancer. Yes. 17 Q. You were questioned a little earlier, and 18 briefly, about the Health Canada assessment. Do you 19 recall those discussions? 20 A. Yes. 21 Q. Okay. And have you had an opportunity to 22 review the recommendations of Health Canada? 23 A. I have, yes. 24 Q. All right. Based upon your review of the 25 Health Canada assessment, what is your understanding</p>	<p>1 A. That is correct. 2 Q. And I believe you spent time today talking 3 with us with regard to the various meta-analyses that 4 you've looked at, examined, and assessed; correct? 5 A. That is correct. 6 Q. Okay. Based upon the totality of the 7 meta-analyses that you have reviewed, what is your 8 opinion with regard to whether or not they demonstrate 9 that talcum powder products can cause ovarian cancer? 10 A. I think that the meta-analyses show 11 consistent conclusions of a 25 to 30 percent increased 12 risk for ovarian cancer; and that coupled with the 13 other criteria that I considered -- the biological 14 plausibility and the various other Bradford Hill 15 criteria -- that I came to the conclusion that talc is 16 a cause of ovarian cancer. 17 Q. Dr. Moorman, is it fair to say that the 18 method -- method of review and your methodology and 19 the analysis that you performed, for purposes of the 20 preparation of your report and the opinions that you 21 shared today, is the type of methodology and the type 22 of process that is generally accepted in your 23 scientific community of epidemiologists? 24 MS. FOSTER: Objection to form. 25 THE WITNESS: I think that the methods</p>

79 (Pages 310 to 313)

Patricia G. Moorman, M.S.P.H., Ph.D.

<p style="text-align: right;">Page 314</p> <p>1 that I used are what I do routinely in my work as an 2 epidemiologist and that is routinely done when we 3 conduct systematic reviews. 4 BY MS. PARFITT: 5 Q. You were questioned numerous times today with 6 regard to the IARC review of talcum powder products 7 and ovarian cancer. Do you recall those discussions? 8 A. Yes, I do. 9 Q. The IARC committee put out a monograph in 10 2010. Is that your understanding? 11 A. That is my understanding, yes. 12 Q. Do you have any knowledge as to when the IARC 13 committee met to make their findings as it pertained 14 to the role of talcum powder products in ovarian 15 cancer? 16 A. I don't recall the exact date, but I believe 17 that it was quite a bit earlier than that. I'm not 18 sure of the exact date. 19 Q. Okay. But it preceded the monograph that 20 came out in 2010? 21 A. Yes. 22 MS. PARFITT: Dr. Moorman, I have no 23 further questions. Thank you very much. I appreciate 24 it. A long day. 25 MR. JAMES: Dr. Moorman, just a handful</p>	<p style="text-align: right;">Page 316</p> <p>1 A. The most pronounced difference that we are 2 aware of is that smoking seems to be more strongly 3 associated with mucinous ovarian cancer than with 4 other subtypes. 5 But in most -- for most other risk factors, 6 there -- the risk factors seem to be pretty consistent 7 across the subtypes. 8 Q. Are you aware that many clinicians consider 9 the various subtypes of ovarian cancer to be different 10 diseases? 11 MS. PARFITT: Objection. Form. 12 THE WITNESS: I think that clinicians 13 recognize that they -- there are differences. Again, 14 going to pathologists, they can distinguish between 15 them. 16 But in terms of how they treat them, it's 17 my -- I'm not aware of any real difference in how they 18 would treat the different subtypes of ovarian cancer. 19 BY MR. JAMES: 20 Q. And other than smoking, which is the factor 21 that you just mentioned, can you think of any other 22 risk factors that have a different impact on a 23 specific subtype of ovarian cancer as opposed to 24 another subtype? 25 A. That is the only one that comes to mind.</p>
<p style="text-align: right;">Page 315</p> <p>1 more questions. Okay? 2 THE VIDEOGRAPHER: Mr. James. 3 MR. JAMES: Oh, of course. 4 Can we go off just for one second? 5 How long did Ms. Parfitt go? 6 THE VIDEOGRAPHER: Going off record at 7 6:22 p.m. 8 (Discussion off the record.) 9 THE VIDEOGRAPHER: Back on record at 10 6:23 p.m. 11 FURTHER EXAMINATION BY COUNSEL FOR THE 12 JOHNSON & JOHNSON DEFENDANTS 13 BY MR. JAMES: 14 Q. Dr. Moorman, since the IARC published its 15 monograph in 2010, we have had the publication of 16 additional cohort data on the talc ovarian cancer 17 association; correct? 18 A. Correct. 19 Q. With regard to the subtypes issue, do you 20 believe that different subtypes of ovarian cancer have 21 different risk profiles? 22 MS. PARFITT: Objection. Form. 23 You can answer. 24 BY MR. JAMES: 25 Q. And I'm talking about in general.</p>	<p style="text-align: right;">Page 317</p> <p>1 MR. JAMES: That's all I have. Thank 2 you again for your time. 3 THE WITNESS: Okay. 4 MS. PARFITT: Thank you. 5 THE VIDEOGRAPHER: This concludes the 6 deposition of Dr. Patricia Moorman. The time going 7 off record is 6:25 p.m. 8 (Whereupon, at 6:25 p.m., the deposition ceased. 9 Signature was reserved.) 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p>

80 (Pages 314 to 317)

Patricia G. Moorman, M.S.P.H., Ph.D.

Page 318	Page 320																																																																																																									
<p>1 ACKNOWLEDGMENT OF DEPONENT</p> <p>2 I, PATRICIA G. MOORMAN, M.S.P.H., PH.D., do</p> <p>3 hereby acknowledge that I have read and examined the</p> <p>4 foregoing testimony, and the same is a true, correct,</p> <p>5 and complete transcription of the testimony given by me,</p> <p>6 and any corrections appear on the attached errata sheet</p> <p>7 signed by me.</p> <p>8</p> <p>9 _____</p> <p>10 (DATE) (SIGNATURE)</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>1 STATE OF NORTH CAROLINA)</p> <p>2) C E R T I F I C A T E</p> <p>3 COUNTY OF ORANGE)</p> <p>4 I, Sophie Brock, Court Reporter and Notary Public,</p> <p>5 the officer before whom the foregoing proceeding was</p> <p>6 conducted, do hereby certify that the witness(es) whose</p> <p>7 testimony appears in the foregoing proceeding were duly</p> <p>8 sworn by me; that the testimony of said witness(es) were</p> <p>9 taken by me to the best of my ability and thereafter</p> <p>10 transcribed under my supervision; and that the foregoing</p> <p>11 pages, inclusive, constitute a true and accurate</p> <p>12 transcription of the testimony of the witness(es).</p> <p>13 I do further certify that I am neither counsel for,</p> <p>14 related to, nor employed by any of the parties to this</p> <p>15 action, and further, that I am not a relative or</p> <p>16 employee of any attorney or counsel employed by the</p> <p>17 parties thereof, nor financially or otherwise interested</p> <p>18 in the outcome of said action.</p> <p>19 This, the 26th day of January, 2019.</p> <p>20</p> <p>21</p> <p>22 _____</p> <p>23 Sophie Brock, RDR, CRR</p> <p>24 Notary Number: 200834000001</p> <p>25</p>																																																																																																									
<p>Page 319</p> <p>1 E R R A T A</p> <p>2 CASE NAME: TALCUM POWDER LITIGATION MDL NO. 2738</p> <p>3 WITNESS NAME: PATRICIA G. MOORMAN, M.S.P.H., PH.D.</p> <p>4 CASE NUMBER: 16-2738 (FLW)(LHG)</p> <table border="1"><thead><tr><th>5</th><th>PAGE</th><th>LINE</th><th>READS</th><th>SHOULD READ</th></tr></thead><tbody><tr><td>6</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>7</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>8</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>9</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>10</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>11</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>12</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>13</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>14</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>15</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>16</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>17</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>18</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>19</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>20</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>21</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>22</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>23</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>24</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr><tr><td>25</td><td>---</td><td>---</td><td>_____</td><td>_____</td></tr></tbody></table>	5	PAGE	LINE	READS	SHOULD READ	6	---	---	_____	_____	7	---	---	_____	_____	8	---	---	_____	_____	9	---	---	_____	_____	10	---	---	_____	_____	11	---	---	_____	_____	12	---	---	_____	_____	13	---	---	_____	_____	14	---	---	_____	_____	15	---	---	_____	_____	16	---	---	_____	_____	17	---	---	_____	_____	18	---	---	_____	_____	19	---	---	_____	_____	20	---	---	_____	_____	21	---	---	_____	_____	22	---	---	_____	_____	23	---	---	_____	_____	24	---	---	_____	_____	25	---	---	_____	_____	
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A				
a.m	access	acknowledges	33:19	11:11 12:1
1:15 8:4 52:16,17	42:19	93:25	additional-mater...	African
52:17,19 115:3,4	accommodate	acknowledging	290:25	7:11 26:9 27:11,12
AACES	14:8	110:12 185:20,22	address	29:1 128:18,20
7:12 29:1,7 128:24	account	186:11 204:13	19:17 35:4 68:12	136:15 283:3
209:4 283:3	176:18 216:14	266:25 270:17	86:23 124:2 135:8	284:16,17,22
284:17 285:6,13	242:20,22 272:4	275:23 276:1	152:3 163:5,19	305:11
285:16 286:25	305:14 309:15	acknowledgment	169:9 171:9	African-American
292:12	accruing	170:8 318:1	172:14 173:25	5:15 20:22 25:21
AACR	295:3	ACOG	176:4 200:3	27:11,15 128:12
5:11 6:18 7:10,13	accumulated	149:9,22	221:10 222:3	135:13 136:8,13
ability	95:7 161:24 178:19	ACOG's	232:11,12	136:17 304:18,24
11:23 35:13 320:8	179:4	5:20	addressed	305:7,13
able	accumulating	acquire	26:5 65:23 66:24	age
72:3 102:23 163:25	142:3 295:9	47:9	119:9 120:15	218:7
248:17 300:24	accuracy	action	122:16 132:7	agencies
abortion	220:4,7 239:16	5:6 280:20 320:14	139:2 153:2	253:10
223:2	accurate	320:17	167:12 172:16	agency
absence	55:23 69:4 81:15	activities	186:5 243:4,7,10	127:5 251:9
83:21	134:4 239:22	10:13,21	303:23	ago
absolute	240:13 249:12	actual	addresses	10:18 136:5 220:19
249:10 287:16	279:3,16 301:15	248:4 274:9	224:7 232:9 244:18	280:19 288:17
absolutely	320:10	add	addressing	291:14 307:11
64:11 70:17 84:14	accurately	16:1 51:20	64:10,11 84:3	310:9
87:20,22 129:7	107:1 136:4 242:17	added	155:1 231:16	agree
165:6 255:11	279:23 300:25	47:24 48:9,19 49:3	311:2	37:17 54:8 56:8
299:6	acetate	50:6 51:5,16	adds	60:23 105:7,12,18
abstract	154:7	161:22 162:5	297:19	106:4 112:7
169:14,15,17 176:5	acknowledge	addition	adequate	129:10 182:12
176:10 195:11	54:18 104:21	217:25 219:10	110:14 154:8,13	190:4 202:10
202:19 205:6,8	106:10,18 109:2	285:6	155:16,17,21	203:10 204:4,12
227:25 264:19	134:1 150:18,19	additional	156:5,8 255:23	204:14 208:18,20
269:11,19 276:16	159:25 193:2,19	4:22 39:1,8,22 40:5	293:2 303:15	210:24 211:2
276:16,24 277:6	204:8 223:16	40:15,22 41:3,15	310:20,23	215:20 233:18
279:9,12	229:24 232:10	43:14 44:21,23	adjective	236:10 238:17
accept	236:24 238:23	46:4,23 47:23	248:14 249:21	245:2 247:1,9
124:22 250:11	239:25 241:18	51:18,20 52:5	advance	250:20 251:2
accepted	247:21 255:13,18	68:11,14 72:22	181:10 184:11	272:25 308:23
111:14 141:23	258:12 264:9	92:24 93:19 95:6	advantages	agreed
251:24 252:3	266:6,9 268:25	95:10 98:1,12	196:23 199:7	223:10
256:13 257:19	271:19 275:11	179:4 189:15,18	advise	agreement
258:20 290:16,23	301:11 318:3	189:23 192:10	168:21 170:1 171:4	239:7
313:22	acknowledged	193:12,16 207:20	advisement	ahead
accepts	23:5,8 107:5	216:14 217:4	25:2	62:9 99:3 114:5
145:5	130:20 131:15	283:17 306:17	afindeis@napolil...	146:16 284:11
	132:8 135:8	315:16	2:14	AHRQ
	231:10	additional-mater...	afraid	127:6

al 5:13,16,19 6:8,10 6:12,17,20,23 7:5 7:9,12,18,21 Alastair 2:14 8:20 12:11 alcohol 182:4 267:22,24 Alexandria 2:4 Alison 5:13 allegation 64:3,7 65:3,17 75:6 105:10 120:17 allegations 9:24 alleged 84:7 86:10 109:19 119:15 122:23 allegedly 105:22 106:9 alleging 106:7 allowable 121:23 122:3 allowed 22:24 alluded 101:8,13 amend 22:18 America 3:2 8:14 280:16,21 280:24 American 5:14 7:11 29:1 128:18,20 136:16 166:12,24 283:3 284:17,22 Americans 305:11 amount 75:20,21 76:5 298:17 299:22,22 Amy 7:8	analyses 75:23 118:7 120:6 120:7 121:16 238:22 239:9 278:17 analysis 5:18 6:19 111:8,12 120:15 121:13 138:23 139:4 179:14,18 182:19 202:21 214:9 215:16 224:14 233:24 236:20 242:24,24 244:3 244:15 256:9 261:14 269:6,23 278:14 279:22,24 283:12 292:3 308:12,21 309:14 313:19 analyze 233:21 242:18 284:7 analyzed 120:15 212:4,5 242:8 287:3 ancestry 26:10 27:12 284:16 and/or 142:25 Anderson 25:18 Angeles 285:4 animal 52:24 58:1,6,11,16 63:4 89:24 309:16 animals 106:24 Anne 44:4 answer 12:22 15:17 22:25 22:25 55:22 57:23 58:8 60:5 61:3,21 62:6 64:22 66:19 69:22 70:2,3 74:5	78:22 82:10,11 95:14 99:2 102:4 125:1,11,25 144:4 163:9,24 171:23 171:25 178:20,20 184:16 200:12,18 200:19,20 201:7,9 201:21,22 204:19 219:1,5 265:1 304:6 315:23 answered 28:18 48:23 50:13 50:15,20,21 54:11 55:18,22 57:15 58:12,15 60:15 61:24 62:23 63:7 63:14 64:20 82:6 82:8 98:10 99:19 125:19 183:4 189:2 190:1 199:3 199:5 200:22 201:17 217:7 219:14 245:24 247:25 248:1 252:19 255:6 267:8 271:12,13 295:19 297:7 300:22 304:12 answering 64:14 65:21 146:22 172:5 219:4 249:4 answers 14:1 60:6 Anticancer 6:13 anticipation 37:4 anytime 14:7 220:18 239:20 apologies 20:14 90:10 96:16 109:11 135:21 146:17 apologize 113:13 148:4 apparently 21:18	appear 265:20 318:6 appears 320:6 Appel 3:15 4:5 8:17,17 294:16,20 295:24 296:18 297:2,22 298:11 299:3,20 300:10 301:14 302:5,11 applicable 230:3,6 282:3 application 6:14 283:18 300:5 applications 272:17,20 276:21 277:11 278:11,21 applied 59:7 63:2 106:11 143:8,10 144:1 300:8 applying 285:12 appreciate 33:1 100:9 314:23 approach 17:25 approached 11:14 appropriate 22:12 47:12 218:19 appropriately 65:23 approximately 8:4 89:6 158:15 April 5:7 44:4 area 57:7 59:4,14 60:18 63:14,17 90:1 106:13 121:22 289:23 areas 56:16,19 60:19 63:3 arguably	210:15,25 argue 274:21 arisen 95:10 98:12 arising 188:13 arrangements 35:15 arrived 302:8 Arsenic 5:9 article 5:11,14,17 6:6,9,13 6:18,21 7:3,6,10 7:13,16 19:20 20:18,20 21:4,19 21:24 22:4,7 23:3 23:25 25:9,14,18 26:2 40:20 59:25 60:1 64:24 65:25 66:3 67:17 108:20 109:18 110:5,18 111:3 147:20 148:7,12,20 149:5 169:13,14,16 170:7,9 174:1 177:21,24 187:20 194:16,18,20 210:9 211:24 212:17 213:16,17 213:20 215:4,4 231:16 235:21 237:8 238:8 239:6 242:16,17 243:6 243:21 254:19 270:2 274:25 276:14 307:20 articles 19:9,14,16 25:10 26:1,4 34:25 35:2 40:10,17 52:4,6 59:12,19 64:9,23 67:13,15 75:10 81:9 88:11 111:24 112:1 166:11,23
--	---	---	---	--

183:21 212:9 213:19 230:11 255:24 articulated 242:1 asbestiform 117:11 asbestos 5:11 19:10 25:11 26:1 28:10 30:10 30:21 31:1 63:20 63:24 64:3,8,18 65:3,18 66:7 67:11 68:12,20,25 69:7,9 70:14,16 70:18 71:2,14,18 71:20 72:2 73:3 75:7,23,25 76:1,2 76:9,15 77:22 79:14,21 81:10,15 81:23 82:13 83:6 83:21 84:7 85:8 86:1,10,13,14,21 86:24,25 87:4,8 87:14 88:1,7,8,12 88:14,21,22 89:1 89:10,17 90:5,19 90:23 91:1,15 92:14,19 93:2,9 93:12 94:19 96:3 103:20 105:2,9,22 106:6,9,14,15 108:7,21 109:14 109:19,21 110:10 111:8,10 112:9 114:6 117:24 119:23 124:21 125:14,21 141:13 141:24 142:13,22 142:24 286:22 287:2 296:16 297:25 asbestos-containi... 105:19 asbestos-contami... 85:14 113:21 asbestos-free	69:1 71:23 asbestos-related 114:19 asbestosis 114:18 ascertained 220:6 ascertainment 210:17 ascribe 257:15 Ashcraft 2:3 15:19 aside 88:21 126:22 asked 34:7 48:22 50:12 50:19,22 54:10,12 54:20 55:15 57:14 58:12 60:14 62:11 62:23 63:6 68:13 82:5,8 98:10,25 99:6 102:10 126:1 129:1 131:16 135:7 140:15 172:4 177:20 178:10,22,24 184:17 195:18 199:2 200:15 201:8,17 206:19 208:14 217:6,13 217:25 218:3 219:3,7,9,11 225:16,22 245:23 247:24 248:2 277:14 286:25 292:20 293:8 297:6 300:21 310:9 asking 12:24 13:10 24:10 29:20 44:15 60:10 60:11 63:2 87:23 134:8 140:12 144:7 146:15,24 201:23 218:9,12 220:10 221:5	223:11 224:24 225:13 250:7 256:23 280:4 288:4 296:24 aspect 211:3 223:23 271:14 279:22,23 aspects 170:15,21 172:14 213:18 309:5 assertion 123:4,8 assess 102:10 202:22 215:2 254:9,18 255:1 278:25 assessed 96:10 110:21 253:11 270:23 276:21 277:11 313:4 assesses 253:4 assessing 64:18 109:13 126:23 127:14,21 196:24 249:15,16 250:7 253:15 256:2 258:22 306:8 assessment 101:17 124:18 143:5 187:16 211:5 217:20 240:9 305:16,18 305:22 306:3,7,11 306:13,22 311:18 311:25 312:14 assessments 159:2 assistant 24:10 288:18 associated 20:21 143:24 147:25 149:2 154:18 155:9 166:7 182:3,9,15	225:8,9 255:21 265:4 303:23 316:3 association 7:10,20 27:5 28:14 90:18 92:13 94:10 94:21 98:14 110:16 127:14,21 132:18,22 133:3 133:16,19,21,23 133:24 134:9,9,10 134:13 135:1,2 136:14 137:7,23 138:11,14 139:17 142:9 148:21 150:24 152:1 155:25 156:4,17 156:22 157:12 158:3,20 160:25 162:3 164:3 169:23 170:13 171:1 174:10 178:16 185:12,16 186:13,17 187:14 188:15,25 189:5 189:10 190:21 192:23 193:5 195:16 200:7 203:22 204:11 205:17 210:19 228:25 234:17 236:20,22 241:5 242:5,20,22 244:9 245:4 246:10,10 246:12,15,18,25 247:1,8,17,23 248:5,9,17 249:5 249:7,11,17,19,25 250:3,10,18,21 251:2,6,11 253:1 253:5,16,18 256:11,14 257:3,7 257:13,15,17 258:19,20,21,25 261:10,14,22 263:25 264:8 265:9 266:3 267:3	267:5,16,23 270:6 275:14 287:15,17 287:18,22 288:7 292:4 293:3,4 298:15 299:25 315:17 associations 94:1 126:13,20,24 136:21 140:3 143:22 162:1 176:19 193:3 230:13 231:14 245:7,13 246:14 247:16 248:25 250:2 251:22 252:2,8,11,16,17 253:13,19,22 257:19,20 258:9 258:10,12 264:11 272:14 287:7,10 287:11,11 288:24 assume 231:12 288:10 assumed 290:18 assuming 297:24 assumption 290:15,22 assumptions 298:7 attached 45:19 46:21 318:6 attempted 22:18 attempting 117:20 attention 23:10 59:13,20,21 59:24 185:9 207:22 232:21 233:1,3,6,18,22 233:25 240:22 attenuated 132:19 133:16,21 134:3 137:24 138:1,4,9 162:5
---	--	---	---	--

234:17 241:1 attenuating 190:21 attenuation 132:9 264:7 266:16 attorney 11:24 320:15 attorneys 11:12 12:3,14,18 13:12,15 attributable 241:14 261:20 attribute 242:4 attributed 270:10 271:2 Austin 2:8 3:4 author 20:19 21:12 22:4 22:11,17 25:16,18 179:6,7 188:21 246:24 247:7 292:12 author's 227:24 277:6 authored 13:8 19:9,14,16 25:10 26:1 37:7 37:15 42:13 287:21 authority 158:18 244:19,23 authors 23:4 108:11,17,19 109:3,25 110:9,12 163:3 166:4 167:18,24 168:7 168:21 169:5 170:2,9 172:21,25 173:17,25 174:6 174:14 175:7,25 176:4,10,21,22 179:3 180:16,24 181:1 183:2 186:12 187:20 188:21 195:10,12	195:19 202:20 203:3,16 204:13 205:7,9,24 206:9 207:10,19,25 208:21 210:12,24 212:21 234:23 247:7 264:21 265:3,4,17 266:2 267:2 269:13 270:4 275:2,15,19 276:12 277:17 279:9 287:23 290:15 authors' 176:24 178:24 275:2 available 33:21 47:16 50:18 51:11,12 67:17 74:16 75:12 88:18 155:23 176:11 Avenue 3:3,8 average 218:7 aware 30:6,8 47:10 48:16 51:12 52:6 59:3 59:12,19 74:20 83:14 86:12 88:10 88:17 102:20 107:19 111:21,24 114:16 119:8 122:15 146:24 147:2,2,20 182:21 183:19,23 184:2 186:20 187:20 199:13,18 200:16 200:25 201:2,8,11 201:11,24 203:24 263:12 285:17,21 292:11 303:6 304:17 316:2,8,17 <hr/> B <hr/> B 3:15	baby 80:10 129:16,23 130:3 back 29:16 35:16 36:5 52:18 61:9,15 103:19 115:5 116:23 123:14 135:12 147:8 150:16 153:15,18 153:22 165:11 177:18 180:8 183:13 204:9 206:22 211:16 215:5 217:15 218:9,13 219:22 232:22 234:5 242:15 248:24 249:24 259:16 264:2,14 269:8 278:5 280:4,13 295:12 302:19 310:1 315:9 Background 202:19 backwards 173:4 BACON 2:17 bad 76:2 baffled 155:20 balanced 240:9 ballpark 229:13 bar 250:19 base 117:5 based 47:2 81:24 87:6 90:20 92:16 93:12 93:14 116:4 117:8 117:9,23 118:6 119:22,25 125:3,4	125:19 129:9 130:21 140:1 144:2 154:17 156:7 198:13 222:17,18 224:20 235:23 240:16 243:23 244:24 274:15 275:6,10 276:6 281:14 296:3,10,20 297:20 298:9 300:18 311:14,15 311:24 313:6 baseline 218:7,19 bases 71:9 117:20 basically 31:20 35:1 181:8 181:16 260:17 basing 116:11 122:17 126:4 154:9 275:10,25 basis 67:25 68:1 122:2 123:20 124:6 220:4 222:13,16 242:11 262:18,20 281:15 batch 72:23 bear 55:4,8 245:6 282:8 beat 151:19 began 60:12 218:22 beginning 108:16 269:12 begins 38:25 207:18 behalf 2:2,16 3:2,11,17 9:21 16:25 beliefs 25:15	believe 12:23 13:2 14:21 18:22 22:3,6 23:23 24:9 30:12 32:9,25 34:7 36:17 40:16 47:4 49:17 50:14 56:21 56:23,24 58:4,14 59:2 63:22,24 64:20 66:13 67:2 75:9,13 79:23 80:5,6,18 81:11 88:22 89:15 108:5 110:10,19 111:2 115:22 118:12 120:13 122:2 123:6 127:8 129:18,22 132:14 136:24 140:11 145:4,8 148:12 164:18 165:18 168:17 177:15 183:14 187:25 188:20 191:8 192:12 193:8 209:6 216:23 217:2 219:5 220:10 234:2 236:1 266:18 272:5 273:11 284:8 291:2,10,23 294:9 303:25 304:8 310:15,19 313:2 314:16 315:20 benefits 206:18 Benign 20:20 Berg 169:1 Berge 6:10 169:1,5 170:2 171:5 172:17,21 172:25 194:18,20 195:10 212:16 213:15,20 214:9
--	--	--	---	---

214:17 215:2,4,12 215:15,17 269:3 270:2 best 43:10 320:8 Bethea 30:1 better 190:5,23 bias 7:14 103:14 110:15 132:23 159:11,16 159:18,18 160:1,4 164:11 176:16 185:7,20 186:6,11 190:10,10 203:7 203:12,23 204:9 204:10 205:14 206:9 207:13 220:23 221:1,7,12 221:13,19 226:11 226:22 229:2,3,14 230:7,12 231:4,4 231:11,12,17,17 231:20 232:5,10 232:13,20 237:17 238:10,24 239:8 239:12 240:1,11 240:16,19 241:6 241:14,19,19,24 242:4,5,8,20,22 243:4,10,17 251:3 251:7 254:10 270:10,15,16 biased 231:22 biases 160:11 164:13 171:13 177:5 230:22 231:23 264:7 266:15 270:17 271:3 BIDDLE 2:21 big 100:1 229:15 binder	4:17 35:7,19 36:2 273:13 biologic 205:12 254:13,15 297:19 biological 48:14 87:11 88:16 117:12 121:4 181:11 182:6 183:10 309:6,15 313:13 biologist 53:21 57:4,18 biology 53:20,22 57:9,10 309:16 bit 12:1,5 59:4,14 134:24,24 143:6 144:13 148:3 154:23 155:20 161:17 234:15 288:20 289:5 291:11 314:17 Black 284:25 blanking 12:12 blogs 30:17 board 293:17 bodies 146:9,25 254:9,12 body 7:10,13 56:22 60:13 63:10 64:18 89:9 102:10,20 103:19,21,24 104:22 105:7,13 105:17 106:19 107:5,13,17 111:15,22 112:17 128:24 129:8,9,13 131:5,17 132:2 142:12,13,22,25 144:15,17 155:13	156:11,21 161:12 174:7 178:12 197:20,25 199:11 199:14 200:16,25 201:12 202:4 227:15,19,21 229:14 231:3,6 237:15 239:15 253:20 254:7 255:1 260:10 262:3 263:18 312:16 Bondy 29:7 borderline 274:20,24 Boston 285:1 bottom 77:18 85:10 108:15 109:23 150:7 167:17,23 195:1 196:21 203:17 207:18 210:13,14 211:23 221:10 226:7,15 272:11 276:17 277:5 Brad 3:23 Bradford 111:8,11 182:21 183:8 244:3,20 247:15 248:24 249:15 258:23 263:9 292:3,8,17 308:12,20 309:5 309:14 313:14 brand 75:11 break 14:7 19:13 52:11 113:10,16 114:24 117:2 165:5 175:18 209:16 210:1,5 211:10 259:10 breaking	259:2 breast 181:24 182:1,2 225:21,23 254:1,5 breastfeeding 154:15,18,20,24 155:2,7,9,15,16 156:12,17,23,25 157:4,13 293:5 305:9 Brennan 2:23 8:11,11 173:13 259:7 briefly 264:14 311:18 Britton 7:15 237:15,25 Broadhollow 2:12 broadly 128:21 Brock 1:21 320:3,22 broken 235:5 brought 23:10 33:25 34:4 35:7 54:24 59:13 59:20,21,24 126:18 221:7 bulk 311:1 <hr/> C <hr/> C 2:1 3:1 5:9 6:22 8:1 320:1,1 cadmium 122:13 calculated 214:20 calculation 214:17,18 215:3 calculations 124:18 212:4,6 California 7:18 285:3	call 110:23 133:9 247:23 called 109:3 282:16 283:24 calls 94:20 Camargo 110:18 111:3 Cambria 1:17 Campus 2:22 Canada 145:16,19,23 146:3 146:8 147:6 150:17 253:14 305:16 306:21 311:18,22,25 312:1,3,14 cancer 5:12,14,17,20 6:3,4 6:7,10,12,15,19 6:22 7:3,4,11,11 7:14,16,17,21 9:19,25 19:10 20:21 21:15 23:5 25:12,16,21 26:9 26:25 27:5,11,15 28:12 29:2,2 30:22 31:1,24 32:12 40:19 48:15 52:3,9 53:20,21 53:22 54:15 56:21 57:4,18 58:17 60:4 62:22 63:21 63:24,25 66:2 87:1,5,12,14 88:23 89:1,11,17 90:19 92:14 93:4 93:9 94:14,19 98:5,14 102:8,13 102:15,24 103:20 104:5,9 105:11,15 108:8,23 109:14 109:22 110:10
--	---	---	--	---

111:9,10,13,23 112:10,18 113:1 114:12 117:14 120:19 121:3,6 122:13,17 124:3 124:24 125:6,8 127:4,4 128:11,19 128:20 135:13,18 136:8 137:1 138:17,20 139:4 139:18,24 140:16 141:12,23 142:3 142:14 143:2,10 143:14,15,21,23 143:25 144:17,18 144:23 145:6,9 146:4,12 147:1,19 148:1,10 149:4,10 149:23 150:12,23 150:24 151:11 154:19 156:12,17 156:23 157:1,3,4 157:13 158:13 160:20 161:11 166:8,20 167:5,6 168:5 174:11 176:16 181:15,18 181:24 182:1,2,7 185:14 186:19 187:7 188:15,25 189:5,10,16 190:13 192:24 193:6 197:1,7,8 197:15,20 201:12 202:23 203:24 205:20 207:23 209:6,9 210:21 212:10 213:1 218:19,22 224:19 225:6,21,23 226:4 226:18 227:17 228:11,17 229:25 231:7 232:7,11 233:13,23 234:24 237:16 245:9,11 245:15,21 246:9 246:24 247:8,19	249:2,14 251:11 252:25 253:12,25 254:1,4,5,8,17 255:8 257:25 259:23,25 260:7 264:1,10 265:5,20 266:3,21 267:22 267:24 270:8 271:25 278:13 283:3,19 285:10 285:17 286:14,20 291:21 292:5,13 292:14 294:25 295:2,4,7,20,22 296:7 297:5,10,14 298:16 299:25 303:2,5,10,14,20 304:2,5,10,19 305:5,13 307:25 309:16 310:12,16 311:2,9,13,16 312:2,5,23 313:9 313:12,16 314:7 314:15 315:16,20 316:3,9,18,23 cancers 5:18 54:15 113:24 138:22 254:5 285:14 capable 248:8 249:19 capture 50:5 59:8 60:13 captured 218:23 carcinogen 96:24 97:3,7,23,24 97:25 98:22 101:23 carcinogenic 96:4,18,22 98:17 99:12,15 119:7 122:19 123:5,24 146:14 180:20 253:3 carcinogenicity 122:23	Carcinogens 5:10 Care 3:11 8:18 294:15 294:20 career 23:6 127:15,22 156:20 295:8 careful 246:2 carefully 186:6 Carolina 1:18 135:18 137:1 138:17,20 139:3 140:16 285:16 292:13 320:1 carries 92:3 207:18 carry 160:5,9 carrying 226:7 case 9:19,22,24 10:2,3,5 11:10,21 12:3 15:10,20 16:18 17:7 31:21 32:20 41:2 45:6 47:2 59:1,8 60:12 74:18 76:13 87:10 106:8 115:20 116:10 119:17 120:8 125:16 152:15 165:24 174:18 175:23 179:8,15 180:12 197:6 216:23 229:8 232:15 268:3 289:10 295:12 305:4 308:25 312:22 319:2,4 case-control 7:7 20:22 170:23 171:11 185:6,21 187:8 195:20,21	196:22 197:8,13 198:2,4,22,25 199:13,22 203:19 205:15 207:13 208:12,18,22 211:7 213:8 214:14 220:20 226:12,21 227:1 227:14,19 228:2 228:14,19 229:1,4 229:11 230:1,8,14 230:17,21 231:15 231:19 232:13 238:11 241:11,18 243:17 264:13 266:19 267:5,17 268:19 270:9 284:9 285:5,5 300:20 301:3,11 301:22 case-controls 198:7,8 269:24 271:6 cases 1:9 6:19 11:13,20 12:2,4 15:20 104:12,13,15 107:15 199:25 200:1 212:14 213:1,3 239:17 261:19 264:5 275:13 284:18 303:10 categories 217:21 categorize 35:2,2 category 140:7 252:12,18,20 258:8 274:4,10,13 275:12 causal 90:17 92:13 142:23 143:18 145:19 146:5 158:3,20 159:2 163:13,15 164:3 166:15,25	168:3,12,17 169:22 170:11,25 174:9 176:13 178:6,15 181:14 182:11,18 185:15 195:15 245:7,13 246:14,15 250:2 250:19 251:24 252:4,7,15,23 253:1 255:15,16 255:22,25 256:14 256:19 257:3,8,19 257:24 258:9,20 259:1 269:16 308:24 309:11 causality 143:9 144:2 149:6 159:7 174:16 182:23 causation 163:4,6 164:8 166:5 168:9,22 169:6,10 170:3 172:21 173:18 174:1 175:8 176:2 176:5,25 177:13 177:21 178:25 181:2,20 183:3 254:21 255:5 256:5,7 257:1 258:1,11,13 310:11 cause 5:11 9:25 31:23 87:12 88:22 98:5 102:8,12,15,23 108:8,22 111:10 120:18 121:2 122:13 124:24 125:8,15 142:15 145:5,9 146:3,12 147:1,18 167:9,15 179:22 182:2,8,16 183:11 294:24 302:24 303:1,19 304:2 307:1,25 308:7 310:12
--	---	---	--	--

311:6,9 312:4,23 313:9,16 caused 166:20 167:3 225:23 causes 5:17 86:25 87:4 105:11 141:12,13 141:23,24 150:11 167:6 181:18 295:4 304:10 305:5 caution 160:15,18 163:15 168:9 240:14 cautionary 164:7,10 caveats 218:4 ceased 317:8 cell 53:2 58:20,24 60:25 61:6 62:3 63:4 156:23 303:13 Central 7:17 certain 39:15 121:2 168:3 168:12 certainly 25:1 52:14 60:18 78:9 86:12 102:5 145:14 211:3 218:11 237:1 239:3 245:8 247:15,16 248:25 249:2 250:17 256:18 257:5 264:12 292:18 certainty 59:15 80:8 102:18 certify 320:5,12 chair 290:1	chance 49:25 103:14 change 10:8,12,19 43:15 43:17 51:21 52:10 111:5 125:22 changed 193:25 changes 10:15,20 18:23 38:12 changing 69:13 characteristics 199:8 characterization 53:17 201:5 247:2 characterize 67:14 97:2,3,6,9 160:8 162:23 184:22 249:8 characterized 49:17 75:25 184:20 charging 14:16 chatroom 30:17 check 21:16 216:23 checklist 101:25 103:8,11,18 Chemistry 85:7 Chicago 3:19 285:6 childbearing 182:4 choose 289:19 chose 288:9 Chris 13:3 chromium 119:12,15 122:13 chronologically 173:4	CI 137:20 138:10 139:20 cigarette 141:11 cite 32:16 95:2,5 146:11 158:18 183:17 192:14 211:24 212:1 213:20 214:1 221:18 222:14 226:8,10 242:7 243:2 244:14,17 244:19,22 246:8 251:9,15 253:4,8 254:2 256:19 273:7 276:9 cited 45:6,25 46:4 51:1 66:20 78:17 123:1 123:3 152:17 183:20,21 206:24 207:3 230:12 246:17 250:8,9 253:23 255:1 273:1,9,21 277:17 cites 104:19 citing 242:12 272:24 279:16 claim 68:20,24 70:22 75:17 102:12 108:7 118:24 119:6 121:11 276:10 claimed 292:4 claiming 198:23 199:1 267:3 267:16 clarified 129:5 clarify 91:21 115:17 120:9	130:2 142:17 144:5 267:21 clarifying 117:9 clarity 16:2 Clarke-Pearson 44:5 290:3,5 classification 103:8 classifications 96:25 252:14 classified 96:11 252:12,17 classifies 155:24 clear 23:14 47:23 91:5 93:24 100:12,14 128:16 130:15 248:13 275:5 276:4 303:13 311:5 clearing 29:22 clearly 90:20 92:15 120:5 143:21 182:1 197:2 236:12 clinicians 316:8,12 clock 200:23 close 137:8,10 138:6,14 265:14 279:25 closed 291:17 coauthor 20:23 25:22 26:7 138:24 292:11 coauthors 28:20 29:9,12,24 30:3,6 239:6 285:15 cobalt 119:12,15 122:13	cohort 7:7 90:21 92:17 104:11,18,19 170:24 171:11,13 185:12 186:13,16 186:18 187:7 188:13,14,24 190:4 191:3,7 192:5,8 194:9,25 195:22 196:22 197:7,13,22 198:2 198:4,20,24 199:12,15,19,24 200:2,18 201:1,13 202:7,10 204:14 204:17 205:7,21 205:25 206:1,5,9 206:18 208:1,6 210:15,25 211:20 212:9,24 213:5,9 214:14 215:18 216:6,17 218:8,16 218:18 220:2,6 226:21 227:1,20 228:2,19 229:5,12 230:2,10,14,18,20 231:23 263:15 266:20 267:4 268:10,19 270:9 270:15,17,19 284:9 285:1,2,3 300:19,24 301:8 301:22 302:1 315:16 cohorts 104:8 198:6,8 206:10 212:2 220:8 263:24 265:24 269:24 271:6 308:25 coin 240:2 coinvestigators 285:15 collaborated 54:6 collaborators
---	--	---	---	--

29:4 colleague 294:11 colleagues 31:9,15,18 32:1,8 127:2 collect 222:19 284:3 285:9 collected 283:10,13 284:5,7 collecting 160:3 collection 233:12 283:14 285:14 college 182:1 column 92:8 94:7 167:17 180:17 203:3,17 210:13 212:20 238:2 240:6 270:3 275:2 combination 46:24 combine 159:8,13 160:9 161:4 combined 140:17 188:22 210:21 215:13,16 244:15 combining 158:25 159:25 160:10 187:4 215:22 come 29:7 72:6 116:17 143:8 144:1 145:16,19 258:23 280:4 309:16 comes 48:17 104:6 198:1 243:7 266:8 316:25 comfortable 65:13 81:18,24	98:4 255:3 coming 138:16 comma 204:21 commenced 36:10 commencement 185:10 comment 153:11 158:7 172:11 211:20 214:22 216:2 305:23 306:3,9 commentaries 212:8 commented 157:12 comments 84:7 212:1 223:12 commercially 75:12 committee 8:21 314:9,13 Committee's 4:18 36:18 common 226:1 261:22 305:6 305:7 commonly 111:16 commonly-cited 232:12 communicate 22:13 24:1 293:16 communicated 237:24 communication 22:16 24:3 communications 12:25 13:11 17:3 25:5 28:1 32:1,6 community 141:22 145:5,8,13 147:18 148:14 149:17 174:3 248:17,19 285:3	313:23 community's 145:10 company 67:20 68:3 71:7 72:1,8,13 82:15 126:24 127:9,12 127:14 comparable 155:14 comparative 5:18 138:23 compare 27:14 154:20 compared 234:23 265:5 269:24 comparing 39:25 132:9 138:3 154:14 227:13 260:18 comparison 7:6 138:2 143:20 247:18 255:12 300:19 301:22 compatible 134:21 compiled 41:24 complain 191:2 complaints 192:1 complete 78:4 171:25 241:21 293:11,13 305:22 306:8,14 318:5 completely 41:12 43:12 227:15 228:12 241:23 299:17 300:25 completeness 44:3 78:9 compliance 282:3 component 115:24 117:15	composition 281:18 comprehensive 41:11 47:3,5 56:11 56:15,22,24 57:12 57:25 58:10,19,22 58:25 60:2,17,24 62:1,17,20 63:3,9 63:16,19,23,23 64:2,6,17 65:5,9 65:11 82:3 156:15 156:18 157:6,15 157:15,20 comprehensively 156:21 comprised 212:25 computer 24:19 concede 159:23 conceded 271:5 concern 161:25 164:14 215:11 218:20 228:23 233:7,9 238:10,21 251:3,6 concerned 177:6 239:7 concerning 25:11 30:17,21 31:1 121:18 concerns 164:2,11 192:8 227:8 238:17 263:16 306:10 conclude 95:9 125:8 147:14 155:15 163:4 169:5 170:9 173:18 176:1 177:12 179:21 229:14 240:25 256:5,7 262:19 266:2 275:19 304:1,9	concluded 96:2 108:11 146:11 146:25 147:13,18 174:15 183:2 252:3 258:11 276:12 295:20 concludes 150:8 181:9 302:12 317:5 concluding 96:21,23 103:14 275:15 conclusion 66:9,12,15 69:15 78:17,21 81:17 92:23 93:8,10,15 95:2,6,12 96:7 109:14 111:5,9 123:9 125:23 141:4 142:23 143:8,18 144:2 145:15,17,20 146:13 147:24 150:16 156:9 163:12 169:7,8 176:9 178:7 179:5 182:18 207:11 226:24 250:20 252:7 257:1 258:24 263:4 265:17 266:7 276:6 303:16 306:25,25 307:21 308:24 309:11 310:21,23 313:15 conclusions 72:2 98:4 108:14 110:12,24 122:18 126:13,25 154:3 155:19 162:25 171:5 177:20 178:25 184:25 185:1,3 193:24 195:9 227:3,24 230:25 277:6 290:17 313:11 conditions
---	---	---	--	--

20:21 conduct 56:10 57:25 58:10 58:19,25 60:2 64:17 65:4 66:14 66:22 82:2 156:15 225:10 291:22 314:3 conducted 56:10,21,24 57:12 60:24 62:20 63:9 63:11 65:11 124:17 157:13,16 222:15 262:11 291:21 320:5 conference 25:8 confidence 134:20 137:17 265:10,12 confident 178:17 configured 17:22 confirm 15:6 146:7 confirmation 185:11 186:13 confirmed 18:12 289:8 conflating 249:3 conflict 23:20 28:2 conflicts 23:8 108:7 110:5 153:4 214:2 305:12 confounder 19:19 20:24 21:6 26:22 28:14 286:16 confounding 103:15 159:12 160:4 176:17 177:5 286:2,10 confusing	16:17 258:4 Congress 3:3 conjunction 22:9 37:6 130:10 135:21 261:2,9 conscious 294:1 consensus 145:10 148:13 150:10,18 consider 26:13 44:21,23 52:23 53:1,4,7,10 53:13,16,19,22,23 54:1 57:5,10 69:19 70:9,10 82:17,22 105:1 111:15 122:25 177:4 198:16,19 212:15 218:4 230:22 250:2,14 250:15 254:12 261:1,5 263:7 301:2 302:4 305:8 316:8 considerable 232:21 233:1 238:13 consideration 218:15 293:24 309:13 considerations 219:15 245:1 249:16 250:22,25 272:2 considered 4:17 5:3 27:17 28:13 35:25 39:2 39:9,22 45:20 47:8,15 49:11,18 54:21 57:2,9,16 58:5,6,16,21,24 59:2 78:24 116:2 127:15,20 152:9 152:14 154:2 158:2,19 186:6	197:24 198:20,21 212:8 213:15,18 221:15 222:1,9,24 240:10,11 243:15 253:17 254:15 260:6 286:15 295:6,21 302:6,9 309:17 312:17,18 313:13 considering 26:15 132:20 179:3 242:3 247:11 253:6,12 261:3 266:12 270:14 272:13,15 279:18 292:7,8 consistency 45:1 161:16 205:10 244:8,12,15 262:2 262:3,4,19 263:6 263:10,10,14 266:19,24 267:20 268:4,13,22 271:5 271:14 consistent 162:7 250:1 262:10 263:8,19,23 267:4 267:11,17 268:20 269:2 306:25 313:11 316:6 consistently 226:23 consortium 26:8,11,12 27:1,9 27:14,18 29:19 30:2 283:25 284:6 284:13 constituent 117:13 121:20,24 122:4,24 constituents 116:3,5 117:8,10 119:23 126:6 129:14 180:21 296:12,16,19 297:4,9,24 constitute	320:10 consulted 149:8 consumers 281:12 contacted 11:5,8,18,24 23:10 284:19,23 291:24 contain 18:10 21:20 70:16 81:15,23 88:8 106:14 129:25 296:12 contained 36:1 71:18,20 87:7 88:2,7,12 125:5,7 125:20 294:7 298:10 container 69:6 70:13 containing 15:5 78:1 contains 40:22 49:20 69:7 contaminants 119:24 contaminate 64:4,8 86:10 contaminated 71:2 75:7 79:21 105:10,22 106:9 112:9 114:6 124:21 125:14 contaminates 64:19 65:3,18 68:20 86:21 contamination 67:12 68:12 71:14 72:2 73:3 75:18 75:20 76:5 79:15 84:8 86:1 109:19 contend 86:21 context 26:21 75:25 87:15 93:11 104:23 105:8	continue 16:16 99:9,25 100:8 207:16 218:5 283:14 285:13 continued 3:1 5:1 6:1 7:1 102:20 139:11 283:12 contraceptive 127:3 222:21 254:1 305:10 contraceptives 254:4 contrary 97:19,23 contrast 223:7 231:7 268:5 contribute 117:14 214:13 contributed 164:15 186:7 contributes 117:11 121:4 200:2 control 5:17 106:25 controlled 166:22 controls 6:20 239:18 308:25 controversial 94:15,21 Convention 83:11 conversation 285:23 conveyed 82:18 conveying 241:9 convinced 111:2 copied 35:14,16 copies 34:16,20 35:25 37:23 55:2 136:10
---	--	--	--	--

139:7 149:25	126:15,20,21	227:9,11 228:3	cosmetic-grade	1:1 8:7 14:3 100:4
165:1 173:11	128:5,6,14,25	233:19 234:3,25	77:24	100:11 116:17
175:21 180:9	129:5,14,17,21,25	235:1,9,12,13,15	Cote	320:3
202:14 227:5	130:5,6,8,9,12,17	235:19 236:22	21:13 29:8 31:12	coverage
234:13 237:18	131:9 132:3,15,16	238:4 243:18	31:12	238:14,18
273:19 307:17	132:25 133:4,17	244:9,10,12 252:4	COUGHLIN	covered
copy	134:17 135:14,19	252:18,23 255:16	3:7	236:24 282:7
14:25 17:16 19:24	135:22 137:8,13	257:15 260:16	Council	Cramer
20:4,7,10 24:25	137:21 138:18	261:3 265:9,22,25	3:12 8:18 294:15	188:20 242:2,16
32:19,24 33:18,18	139:13,18,19,20	269:4,17,21,25	294:21	243:3,6
36:11,25 37:9,15	139:21,25 140:4,5	271:7,21 273:1,5	counsel	create
37:22 41:15,19	140:7,14 141:5,8	273:10,23 274:1,5	8:6 9:5,12 12:7	231:5
45:5 49:10 54:23	141:9 144:10,19	275:16 276:10	13:18 14:25 17:23	creates
77:3 84:22,23	145:6 147:13	277:20 279:9	20:3 22:23 33:17	190:10
91:12,14 147:9	152:23 159:9,10	281:17,25 282:4	34:15 36:11 40:14	credible
149:22 151:6,7,10	159:11,12,16,19	283:6,21,22,25	41:24 44:12 46:25	66:6,13 69:14
153:15 165:14	159:20 160:1,6,21	286:3,12 288:11	48:21 49:4,7,25	70:15 71:14,22
293:23 307:13	160:22 161:1	289:10,14,15,17	59:22 67:21,23	75:17 81:2,8,11
cornstarch	165:24,25 166:2,3	289:18 293:20,24	68:5,8 72:10,15	81:14,22
129:18,23,24 130:4	168:7,10,18	296:5 298:25	72:21 74:14 77:4	credit
130:5 131:3,8	169:14,24 171:2	299:10,25 301:18	82:17 83:17 84:15	69:18 70:8
correct	174:2,12,18,24	306:18 308:7	84:24 118:22	crediting
9:19,22,25 10:1	175:1 176:5,21	309:2,11 312:10	145:25 163:25	193:11,15
11:3 17:7,11	177:10,11,22	312:25 313:1,4,5	280:15 289:17	criteria
18:14,14,20 19:6	179:1,8,16,20	315:17,18 318:4	291:2,16 294:14	143:8 144:1 184:9
21:21,22 22:23	180:12,13 181:2	correcting	302:21 310:3,8	244:20 245:3,5,10
23:15 27:6 33:15	182:19 183:3	160:13	315:11 320:12,15	245:20 246:3,5
35:8,9 37:7,8	184:17 185:21	correction	counsels	249:16 255:25
38:22 40:25 42:17	188:15 189:1,5,7	17:14,17 18:6,19	14:16	292:8,17 313:13
43:23 45:13,14	189:10,11,12,13	23:24 49:15	count	313:15
51:3 54:17 55:19	189:16,24 190:5	corrections	151:18	critical
57:9 62:4,22 65:5	191:15,18,20,21	18:23 318:6	COUNTY	261:1,5
69:19 72:15,23	191:24 192:6,11	correctly	320:2	criticisms
73:4,7,12,13,17	193:7,8,13 194:6	78:2 132:24 196:3	couple	214:18
73:18 80:12 85:8	194:13 195:1,2,4	214:21 228:11	55:3 89:4 113:15	critique
90:5,6 93:11,15	195:5,7,8 196:11	274:7 276:23	187:23 240:18	193:9
93:20 94:1,21	196:16 198:9	277:15,16 298:20	243:25 291:3	critiques
95:18,19,21 96:22	202:25 205:4,5	correlates	coupled	219:6
96:25 97:1,4,5,7,8	206:1,25 207:8,9	25:19	313:12	cross
97:10,11,13,20	208:2 210:10,11	corresponding	course	137:19
98:8,17 99:13	211:21 212:2	22:10,17	76:6,12 95:8	CROSS-EXAMI...
100:23,24 101:14	213:21 216:7,12	cosmetic	149:19 156:20	280:15 294:14
103:10,22 107:6	216:15,22 217:1,5	6:14 9:25 77:25	157:2 162:16	310:3
108:1,4 109:4,15	217:10,11 218:2	79:12 85:15 112:8	255:19 299:14	crosses
110:6 112:12,24	219:13 220:9	112:11 114:9,14	301:10 309:14	134:6 137:12
117:17 119:12,18	224:18 225:17	114:17 120:18	315:3	138:11 139:20
120:9 123:20	226:5,8,9,18	210:19 223:17	court	crossing

134:7 137:20	27:10 39:2,9,22	282:19,25 283:9	103:2 258:9	313:8
Crowley	47:6 57:6 85:17	295:5 314:16,18	declares	demonstrates
44:6 120:8 123:15	89:14 95:6 114:16	318:10	103:13	161:16
124:11,12,14,17	114:22 121:1	dated	decrease	deodorizing
Crowley's	124:2 125:3,4	5:5,7	225:1 274:9	129:20
120:10,11	134:13 136:25	dating	decreased	department
CRR	139:3 140:16,17	295:11	154:19 225:9	31:15,18
1:21 320:22	142:2 143:10,13	David	deemed	depends
cultural	143:14 144:2	44:5 290:1	243:16	114:1
25:15	154:12 158:9,25	day	deeply	depict
cumulative	159:8,14 160:1,3	17:24 37:11 99:10	244:12,20	301:20
274:4 275:7,16	160:10,11 161:4	294:6 314:24	Defendant	DEPONENT
276:3,13 277:19	161:11,22,24	320:18	3:2,11,17 11:13	318:1
278:16	162:16 166:17	day-in	280:15	deposed
curiosity	176:11 178:18	126:12	Defendants	9:18 10:2,5
44:18	179:4 182:22	day-out	1:16 2:16 8:10,12	deposition
current	187:21,23,25	126:12	9:6,12 280:20	1:11 4:11,15,19 5:4
88:14 174:7 238:9	188:18,22 189:2	days	294:14 302:22	8:5 9:11 10:9,13
285:8 292:2	190:12,14 192:15	145:24	315:12	10:21,24 11:3
currently	194:9 195:3,6	DC	defense	12:6,15 13:22,23
26:4 79:12 85:16	196:11,16 197:22	3:14	73:25 74:8,15,17	19:1,2,8 20:3
90:4 285:13 286:1	197:25 198:3	deal	defer	22:19 23:3,5,15
305:19 306:3	199:15 200:18	116:16 229:15	120:2 296:19,24	25:11,14,25 30:22
Curriculum	201:1,13 202:8,10	268:22	297:3	31:2,4,7 32:11,20
4:13	204:14 206:1,19	dealing	deferring	33:7,10,25 34:5
cursor	208:1,15 216:14	227:16	120:5 297:16	34:18 36:13,19
43:13	222:19 224:4,6	dealt	define	38:10 47:18 48:5
Curtis	233:11 235:5	310:15	190:17 287:15	48:10 56:3 289:6
40:1	236:3 238:3	decades	defined	291:4,11,12
cut	240:10 242:18	131:7 162:11	184:10 249:22	292:22 317:6,8
14:22 307:12	245:15 263:1	208:16 220:19	282:25 283:2	depot
cut-point	266:8 267:10	243:25 262:15	defines	154:7
287:17	270:19 274:1,8	December	37:17	deps@golkow.com
CV	279:5,16,17	153:20	definitely	1:25
19:25 20:4 21:3	283:10,12,14	decide	146:5	depth
25:13 29:6 33:19	284:3,4,7,15	172:10	definition	63:16
cytotoxicity	285:9,14 287:3	decided	248:4,13,16	describe
53:5	293:2,5,11 297:14	97:16	definitions	27:9 52:5 137:2
	297:20 298:9	decimal	33:14	155:17 157:18
D	303:15 307:24	274:21	degree	159:6 162:20
D	309:16 310:20,23	decision	89:15 157:8 242:18	166:6,15 181:25
8:1	311:14 315:16	108:21 109:4	delays	193:20 194:2,4
Dan	date	187:24 188:7	25:15	197:11 198:10
242:2,16	8:3 14:20 132:2	decisions	Delores	217:19 223:6
Daniel	133:4 163:1,4	193:18	5:18	229:16 249:12
44:5 290:2	174:12 191:12,12	declared	demonstrate	253:3 256:15
data	235:6,8,12 242:17	100:22 101:17	263:25 268:13	261:21 277:13

287:6 288:24 293:9 described 21:6 22:10 27:4 31:13,20 33:24 39:21 75:12,14 107:15 166:10,11 180:4 243:5 251:10 260:8 263:14 285:11 288:6 301:9 describes 71:7 263:10 describing 26:8,11 27:14 29:19 48:13 147:23 215:15 216:16 251:12 description 4:9 5:2 6:2 7:2 286:17 descriptors 289:3 design 169:21 195:14 196:8 197:1,16 198:14,23 208:11 227:2 231:9 263:11 268:14 269:7,15 271:2 301:2,5 302:2 designating 96:20 designed 284:2 designs 199:6,6 231:1,2 desirable 190:8 desire 208:1 Despite 205:10 detail 39:18 43:12 44:3 57:19 64:1 154:23 157:9 188:6	193:20 194:3 214:19 242:3 253:24 254:8,16 255:7 260:8 292:18 307:7 detect 83:5 213:5 detectable 70:14 detected 75:23,24 82:13 determination 299:22,24 determine 43:7 98:16 99:12 103:9 108:21 121:14 225:14 226:22 300:24 determined 283:5 298:23 299:9 determining 249:17,19 detracts 169:21 195:14 269:15 detriment 166:13 167:1 developed 41:7 101:14 131:6 218:21,22 development 94:13 diagnosis 25:16 differ 67:3 161:9 228:1 271:7 difference 39:7 86:16 100:1 105:12 226:25 316:1,17 differences 106:17 171:12 188:3 214:13 231:25 316:13 different 23:4 44:2 45:21,25	52:7 56:16 57:20 86:12,15 95:11 98:7 105:9,16,16 105:21 106:7,11 126:19 131:11 143:4,5,6,11,11 143:11 144:12 146:21 179:5 190:17 195:23 196:8 227:15,22 228:12 231:2 262:12,13,14,23 270:24 287:5 288:16 315:20,21 316:9,18,22 differently 141:3,19 142:4 144:13 difficult 72:6 74:2 221:1,2 difficulty 65:21 direct 55:5 307:19 direction 155:8 262:22 263:20,22 264:13 266:14,24 267:9 267:20 268:23 269:1 directly 19:17 60:21 122:16 232:11 281:12 disadvantages 196:24 199:7 disagree 150:15 155:25 156:8 201:4 208:12 209:3 214:8,10 215:20 215:23 247:1,4,5 247:9 279:9,13 disappeared 194:12 discerning 248:9 disclose	22:6,8,10 27:22 28:17 disclosed 21:11,13 23:12 24:8 27:20 28:16 285:20 disclosing 24:7 disclosure 21:8,17,17,20,23 23:11,22 24:2,12 25:5 27:24 28:2 disclosures 22:18 23:7 discovered 88:10 discuss 22:11 28:9 109:25 152:22,25 191:7 217:8 220:1 224:9 225:2 232:19 234:3 256:3 260:20 262:6 discussed 16:23 25:6 28:8 31:8 50:9 76:17 89:20 107:20 112:23 138:25 146:13 152:17 159:23 186:12 216:13 235:19,20 240:17 253:2 260:6 263:2,16,21 264:6 266:15 269:13 282:21 285:21 296:13 297:11 300:11 305:17 306:21 309:5 discussing 178:23 179:7 224:23 238:4 301:16 discussion 21:12 85:7 107:14 108:3 156:10 177:18 219:21	239:1 271:17 287:4,12 300:13 300:19 302:18 304:22 308:6 310:13 315:8 discussions 32:10 311:19 314:7 disease 107:12,16 110:13 141:13,24 167:2,3 261:19 diseases 114:19 253:7,13 254:25 257:22 316:10 dismiss 257:7,12 dismissing 257:11 disparity 229:25 231:5,8 236:9 dispute 220:4 distinction 131:13 135:1,4 215:14 220:23,25 223:21 235:22 278:22 distinctions 12:5 distinguish 11:24 303:2 316:14 DISTRICT 1:1,2 DMPA 154:7 Doctor 29:22 91:10 109:11 110:3 131:23 163:8 194:21 232:3 264:14 295:25 document 1:9 5:8 33:10,15 64:11 67:17 76:16 76:17 77:12 84:11
--	---	---	--	---

124:8 127:9 145:21 146:6 147:6 152:3 291:1 documents 34:2 64:10 67:16 67:19,20,23,24 68:3,4,10,11,14 68:15,18 69:2 72:1,7,8,9,14,14 72:19,22,23 82:13 82:15,18,23 126:25 127:8,13 127:14 145:23 146:3 152:20 doing 10:18 21:13 31:13 31:15 206:4 222:18 227:12 239:9 243:23 285:13 292:7 domain 47:16 48:1 Donath 3:9 8:15,15 69:10 173:12 Dorota 7:4 dose 272:15 273:4 298:16,22 299:9 299:14 300:7 dose-response 35:4 156:24 271:16 271:17,20,24 272:6,9,14 273:9 273:21 274:16 275:6,16 276:3,4 276:13 277:6,18 279:13 dozen 30:3 89:6 dozens 40:21 125:22 Dr 4:23 8:5 9:8 19:24 21:5 29:7,7,8,25 31:12,16,16 33:3	33:6 34:15 35:17 35:23 36:20,24 37:4 38:20 41:16 41:20 42:2,5 45:4 49:14,24 52:21,23 55:14 56:6,8 57:25 60:10 61:3 61:8,14,19 64:14 67:12 69:22 73:14 73:17,19,23 74:3 74:19,22 77:1,12 78:17 80:11 84:2 84:22 85:2,4 90:8 91:5,11 92:1,5 94:6 95:16 107:25 108:14 115:8 117:2 118:10 119:11 120:8,10 120:11 124:11,12 124:14,17 128:3 128:16 130:15 136:6 139:10 140:19 144:9 150:3 151:9,22 153:10 157:22 165:14,22 167:16 171:16 172:12 174:20 175:13,21 180:11 184:24 195:12 196:20 200:11 201:9 202:18 209:23 211:19 218:24 219:25 234:16 235:4 237:21 238:3,17 239:5,24 240:4 244:1 245:25 246:3 247:15 251:15 257:10 259:19 260:20 262:2 264:17,25 269:11 273:12 274:8 280:1,18 284:19 290:5,21,21 291:4 291:5,8,8,10,11 294:17 296:5	301:15 302:6,12 302:24 304:17 307:18 308:11 309:18 310:5,9 313:17 314:22,25 315:14 317:6 draft 26:13,16,17 28:6 28:15 283:24 285:25 286:7,11 286:15 305:18 DRINKER 2:21 drive 2:22 3:18 33:22 dropping 148:3 Duces 4:16,20 due 132:22 163:8 203:22 228:25 229:1 231:11 241:5 251:7 DUFFY 3:7 Duke 10:10 290:4 duly 9:3 320:6 duration 187:17 217:14,20 218:2 219:13 220:14,15 273:23 274:5,17 275:6 Durham 1:17,18 Dusts 5:9 <hr/> E <hr/> E 2:1,1 3:1,1 8:1,1 319:1 320:1,1 earlier 50:9 57:4 101:13 107:15 130:20	132:11 192:13,20 194:3 216:13 234:15,19 235:19 235:20 263:2 269:3,13,20 281:14 285:24 286:6 287:5 289:8 291:1 292:23 297:17 298:4 300:11 305:17 308:6 311:17 314:17 early 142:2 161:20,25 208:7 editions 288:16 editor 21:16,18 22:12 23:21 24:6 32:15 editorial 24:10 237:7,15,21 237:25 238:7 293:17 educate 78:13 education 181:25 educational 181:23 effect 25:14 103:6 154:9 155:8 180:20 190:20 226:25 262:22 263:20,22 266:15,25 267:9 267:20 268:23 269:2 effects 86:16 105:3 207:22 efficiently 40:5,8 43:7 effort 10:17 50:5 82:2 127:9 131:13 233:21 257:14 eight	240:7 272:24 273:1 273:3 302:14 either 52:6 80:21 113:8 148:24 160:11 215:3 255:21 291:6 Elba 1:17 elements 121:20,24 122:4,24 elevated 133:7 186:7 242:11 eliminate 159:17 203:6,13 eliminated 132:19 133:16,21 133:23 134:2 137:24 234:18 241:2 eliminates 203:12 ELLIS 3:18 eloquently 166:11 email 24:3,4,6,9,16,22,25 emails 17:2 24:5,14 32:6 embarrassed 223:25 224:3 emerged 174:14 emotions 223:4 emphasis 162:19 emphasize 51:18 186:12 197:22 203:4 206:4 302:3 emphasized 199:14 200:17 201:1,13 202:3,9 emphasizes 202:5 248:25
---	--	---	--	--

emphasizing	89:3,16 90:1	equal	evaluating	255:2,23 257:4,8
205:25	106:23 107:3	197:9,11	78:25 142:14	259:22 260:11
empirical	119:8 125:3,4,22	equate	158:11 261:7	271:10 293:3,3
224:4,6	134:5 138:23	183:11	evaluation	295:9 296:15
employed	163:6 166:10	equating	183:8 198:14	297:12 300:12
290:16 320:13,15	182:10 197:25	144:15,22,22	255:25 284:4	302:25 303:25
employee	207:20 224:21,23	equivalent	285:10	304:8,15 307:3
320:15	233:12 243:23	142:13,18 181:20	evening	312:13,15,16
employment	248:16,18 253:5	181:21	35:13 280:18 310:5	evidence-based
10:8	260:3,12 263:1	errata	310:6	159:4,5
employs	296:3 297:14,20	4:11 17:17 18:12	event	evident
281:25	298:9 299:13,19	318:6	36:5	278:17
ended	303:22 304:3,14	especially	ever-users	evokes
219:4 283:8	309:1,7	142:2 185:8 284:15	278:18	223:3
engaged	epidemiological	ESQ	every-use	exact
27:25 30:16 31:25	5:18 131:6 174:8	2:5,9,14,19,23 3:5	264:22	46:17 89:5 103:11
engagements	176:20	3:9,15,20	evidence	191:12 277:19
30:25	epidemiologist	establish	44:21,23 56:25	282:25 283:9
enrolled	41:8 60:17 62:16	174:9	66:7,13 67:8 69:4	314:16,18
208:6	126:8,11 138:12	established	69:8,14 70:12,15	exactly
enrollment	167:4 174:21	90:20 92:15 168:6	70:17 71:14,19,22	40:9 102:24 103:17
218:8	179:12 248:8	168:10,13,14	75:18 81:3,8,11	105:4 112:21
ensure	249:18 261:17	179:10	81:14,22 82:11	118:19 232:2
24:21 127:7	287:14,19 314:2	estimate	85:13 87:9 95:10	307:5
entered	epidemiologists	16:14 72:5,7	98:12,13 100:25	examination
282:16	141:2,18 166:14	221:13 267:25	101:1,8,13,18	9:5 157:14 302:21
entire	167:7 250:9	272:16	102:1,6,7,8,14	315:11
89:9 91:19 253:20	290:22 313:23	estimates	108:24 110:14	EXAMINATIONS
256:16	epidemiology	7:6 226:25 228:1	138:14 141:11	4:1
entirely	5:14 6:6 7:12 29:2	229:5 230:9,17	142:4,9,12,13,23	examine
132:22 188:1 241:6	56:18,20 62:21	231:21 232:14	143:1 144:13,16	27:1 272:14
entirety	63:11,17,20 66:1	296:25	144:18,22,23	examined
42:25 43:1 85:22	106:21 119:5	estimation	145:14,15 150:17	9:4 114:14 186:19
entitled	128:19,20 197:15	258:8,8	152:1 154:8,13,15	205:18 313:4
41:15 85:6 92:4	250:17 278:24	et	154:17,20,21	318:3
135:12 136:7	281:16 283:4	5:13,16,19 6:8,10	155:14,16,21,22	example
138:22 237:15	286:23 287:7	6:12,17,20,23 7:5	155:25 156:3,7,8	39:25 48:12 74:18
environment	288:10,14,15,22	7:9,12,18,21	156:11,16,22	112:11 114:3,6
105:20	epidemiology-foc...	ethnic	158:3,20,24 159:7	141:20 142:5,21
environmental	289:22	262:14	168:17 169:6	142:22 154:4
90:25 93:1	epithelial	evaluate	174:8,13,16 176:1	158:23 159:17
envisioning	6:15 7:17 176:15	224:15 233:3	178:5,12,15	167:14 171:12
301:17	278:12 303:5,14	286:19 293:11	199:21 205:12	181:22 199:23
epi	310:16 311:2,13	evaluated	207:7,20 208:4,19	209:4 223:1
182:15	311:15	126:19 293:5	208:23 209:11	228:16 245:9
epidemiologic	epithelium	evaluates	226:3,11 241:20	282:24 293:4
34:25 45:3 47:6	94:13	293:2	246:13 254:20	296:14 297:13

examples 141:8,16,21 142:20 144:10,11 245:13 256:13,18 257:9 257:18 258:25 296:21	42:25 45:7,8 49:10,12,16 50:1 61:15,17 76:24 77:2,17 84:20 91:14,17,21 107:22,23 136:7 136:11 139:6,8 149:22,24 151:13 164:21 165:2,3,18 169:2,3 173:9,10 175:17,19 180:6,7 194:21 202:14,15 204:25 205:1,2 209:24 210:2 212:17 227:5,6 234:6,10,11 237:14,19 264:15 273:16,17 276:15 291:1 292:22 307:14,15	experience 106:5 224:20 experiencing 105:20 experimental 166:17 174:7 expert 4:21 10:23 11:6 21:10 26:6 31:21 37:7 42:20 43:18 43:22,25 44:13 52:24 53:1,5,7,10 53:13,16,19,23 54:1,7 56:9,10 66:5 73:3,25 82:17,22 88:3 101:16 124:15 127:21 139:1 174:17,21,23 179:7,11 197:6 289:19 290:11 291:3 292:6 293:22,23 294:4 294:24 295:11 302:7,8 expertise 41:7 54:4,9,13,16 54:21 55:15 56:3 56:16,17 57:3,7 57:18,20 58:23 59:4,14 60:18,21 63:15,17 83:4 90:2 121:22 289:23 experts 16:24 17:3 30:6 44:17 60:20 73:6 73:7,12,22 74:18 271:4,7 289:9 290:19 296:20 297:3,17 explain 39:7 88:15 110:15 204:9 215:24 explained 241:21 explains	231:13 explanation 192:19 204:10 213:11 215:18 241:22 305:3 explanations 231:24 explored 88:25 exposed 105:14,18 213:2 262:1 275:12 287:2 297:21 exposure 5:11 7:17 48:15 87:3,6 88:16 90:18,23,25 92:14 92:18 93:2,12 94:10 105:2,4,8 105:10,13,16,17 105:21 106:4,8,12 106:15,25 108:22 116:4 143:6,22 151:25 176:14 182:7 187:17 189:19 190:9,19 191:14,16 197:19 204:1 208:9 210:18 211:4 217:19 218:9,13 220:1 221:2,25 238:12 240:22 251:21 259:24 260:7,21 261:2,6 261:13,20 270:23 270:24 274:10 300:6,24 303:22 311:7,8 312:1 exposure-disease 158:11 exposures 106:10 126:19,24 128:21 191:25 220:11,18 221:5 223:6 251:16 252:11,21 253:7 253:13,17 254:14	254:25 255:13,14 255:19 256:4,16 257:4,22 express 119:17 expressed 124:5 168:22 169:12 170:3 expressing 31:22 32:7 expression 25:24 extent 31:10 44:8,11 114:13 160:2 163:24 233:22 external 300:5 extra 37:23 77:3 84:23 165:19
<hr/>				
F				
<hr/>				
F				
3:9,13 320:1				
fact				
51:15 79:3 96:22				
104:22 111:21				
112:9 125:22				
132:18 135:17				
163:14 169:9				
173:25 176:4				
178:6 192:14				
194:9 237:4 256:3				
267:22 270:6				
294:1 298:22				
factor				
28:12 114:15				
151:25 155:24				
166:16 181:20,25				
182:5,7,25,25				
183:1,7,11 187:21				
192:9 196:25				
224:15 232:19				
233:4 255:22,22				
261:21,24 286:2				
286:11,20,22				

292:16 295:7,20 295:21 296:7 297:5,9 305:10 316:20 factors 5:15 19:11 23:4 25:12 26:12,15,25 27:10,15,17 30:22 31:2 135:13,24 136:8 141:3 145:1 167:2 181:17 182:3 183:9 214:12 225:7 243:9,11,15,16 244:3 247:11 249:15 250:2 285:10 286:19 305:6,9,15 316:5 316:6,22 factory 105:19 fair 15:12 34:13 40:24 42:11 43:3 49:22 61:5 95:25,25 126:9 137:13 138:8,8 151:8 161:12 162:19,20 162:23 170:17 229:16,21 260:10 274:15 291:11 313:17 fairly 10:19 41:11 fall 134:16 300:19 fallopian 6:3 151:10 298:19 298:23 299:10,15 299:23 300:7 falls 301:17 familiar 13:24 45:10 103:11 111:7,21 157:7 173:6 237:22 far	118:1 212:20 Faries 2:9 8:22,22 12:11 38:3 77:6 259:6 fashion 243:4 Fathalla 40:19 fault 100:16 fax 1:24 FDA 5:6,7 76:13,16,25 77:21 80:3,14 81:4 84:3,6,23 85:8,11,25 86:5 290:2 FDA's 77:18 feasible 299:16 feedback 222:19 feel 21:18 39:18 65:13 81:17,23 82:7 178:17 223:25 224:3 255:3 262:4 felt 51:17 98:4 110:13 111:13 184:5 223:14 306:13 fewer 255:24 fibers 75:23 77:23 Fibres 5:9 fibrous 115:9,21 116:6,9 116:12 117:6,16 117:22 118:5,18 118:25 119:6 126:2 field 147:22 243:24	288:11 figure 17:25 194:23 269:21 figured 196:5 finally 16:21 financially 320:16 find 44:23 46:11 50:10 52:8 60:11 113:23 130:16 134:23 162:3 187:2 200:7 225:17 272:18 273:5 275:5 277:23 279:4 Findeis 2:14 8:20,20 finding 71:19 267:5 findings 73:23 74:19 81:4 85:7 131:7 152:23 152:25 198:15 214:13 262:10 267:1 302:7 314:13 finds 277:18 fine 23:1 28:19 35:18 78:10 153:11 280:2,7 finish 61:14 77:9 113:9 113:11,12 152:7 172:9,11 186:3 209:17 finished 146:20 148:6 159:15 284:10 289:13 first 9:3 11:5,8,14 20:19 25:16,18 29:15,16	72:23 90:11 92:8 116:9 128:4,6,10 137:25 142:21 169:13,15 181:8 185:2 188:21 200:20 210:8 211:23 221:24,24 233:7 244:11 260:8 262:6 264:18 270:3 276:16 282:14 289:24 291:22,23 294:23 fish 234:9 five 92:16 217:21 252:11 254:13,25 255:13 273:3 277:18 fix 77:9 210:4 flaw 184:22 flawed 160:4 flaws 184:2,21 Fletcher 48:13 flip 18:9 49:25 flipped 151:18 flipping 49:20 Florham 2:22 flow 113:8 FLW 1:7 319:4 focus 19:17 135:23 292:14 298:8 303:11 focused	27:13 66:3 109:21 128:11 157:4 240:22 focusing 112:4,25 folders 164:5 folk 25:15 follow 13:22 191:17 294:22 300:25 310:7 follow-up 113:6 187:18 189:15,19,20,22 190:4,8,22 191:3 191:13,23 192:6 192:10 193:10,12 193:16 194:10 208:10 216:1,6,9 216:10 217:1,4,10 217:12 218:22 219:7 220:8 followed 189:22 208:8,10 217:23 237:8 300:3 following 185:9 233:4 follows 9:4 33:15 277:7 footing 197:9,11 footnotes 272:25 foregoing 318:4 320:4,6,9 forest 194:24 268:6 forgotten 220:16 form 12:21 22:20 26:16 26:17,23 27:7 28:6,15 41:5 42:15,18 45:23
---	---	--	--	--

46:8,14 47:19	283:24 285:25	fraction	furnish	277:8 278:11,18
48:3 49:5 51:2,24	286:11,15 287:24	49:7	44:13	278:21 279:14
58:3 59:10 62:8	294:23 296:23	fragrance	furnished	genotoxicity
63:6 64:5 65:6,15	297:6 299:1 300:1	123:20,23 126:2	15:1 42:6	53:11 60:3,9
65:19 66:18 67:6	305:18 306:5	fragrances	further	gentlemen
68:6,22 71:15	307:2 309:3,12	119:24 120:12,14	117:10 158:8	69:25 311:4 312:24
72:17,24 73:8	313:24 315:22	123:14 124:6	226:11 302:21	geographic
74:10,25 76:7	316:11	296:13,21	314:23 315:11	262:13
80:23 81:6,20	formalized	frame	320:12,14	geologist
82:5,19 83:12,22	292:10	11:17 132:10,11		82:21
84:9 86:2,14	formally	143:12 179:1	G	geology
87:14,16,24,25	33:10	frames	G	53:24
88:1,4 89:2,12,21	format	143:5	1:12 4:10,15,19,21	Gerel
91:7 93:16,21	24:2	framework	5:15 8:1 9:2	2:3 15:19
94:22 95:3 96:5	formed	182:21,22	318:2 319:3	Gertig
97:14,21 101:3,21	26:10 51:10 88:17	free	Gates	7:5 189:4 190:14
102:16 104:1,24	125:3 295:3,15	79:14	187:21 189:9	193:21 194:12
105:24 107:7	296:6	frequency	190:12 192:14,23	195:7 204:25
109:5,16 110:7,25	former	272:16 273:4,23	193:6,12 194:9	getting
112:13 113:25	270:11,16 290:1,2	274:4,17	195:4 216:15	144:19 222:19
114:20 115:15	formerly	frequently	217:5	237:3 258:16
116:1 118:1,16	290:4	53:22 166:14	general	279:25
119:1 122:6,14	forming	183:24 230:12	41:10 94:19 109:15	Gibson
123:10 124:25	76:12 152:15	305:11	124:23 125:15	11:7,17 12:13
125:17 126:3	175:23 290:17	FRIDAY	145:7 147:1 190:7	girls
127:23 129:6	296:7 297:23	1:14	203:10 204:5	93:1
133:5,11 134:18	299:8	front	243:23 287:12	gist
137:9 145:11	forth	45:12 61:9 136:2	301:6 302:24	119:21
148:15 149:18	103:10 214:9	147:9 148:23,24	303:1 310:10	give
157:17 161:2,18	Foster	273:13	315:25	19:22 69:17 70:7
162:14 170:4	3:5 4:4 8:13,13	full	generally	72:5 90:9 113:15
171:7 175:9 176:6	280:8,17,19	92:8 94:8 105:20	102:15 161:11	132:5 141:20
177:14 178:9	281:23 288:2	128:4 132:20	190:23 199:14,22	152:4 158:24
179:9,23 181:3	294:10 313:24	138:3 157:25	200:17 231:14	181:21 187:2
184:4 188:16	found	170:19 183:8	251:24 252:3	223:1 241:20
189:17,25 190:6	77:22 81:10,25	204:10 233:7	256:13 257:19	245:12 294:7
190:15 192:25	82:11 120:25	260:8,24 262:6	290:16,23 301:2	298:14
193:14 194:14	130:11,16 131:19	270:4 275:1	304:17 313:22	given
196:12 197:23	134:22 136:4	305:14	generate	30:20,24 33:1 60:6
201:15 207:1	166:20 187:13	fully	52:4	107:14 116:8
213:22 214:4	194:12 203:19	193:2 247:20	genital	117:19 188:10
228:15 229:18	225:25 272:9	funded	6:9,18 106:13,15	318:5
236:11 247:3	278:12	209:7 283:20	132:1 180:19	gives
255:17 258:2	finds	funding	213:2 222:8	134:20 240:9
266:5 267:6,18	307:20	283:8,14,17 285:12	223:18 224:3	giving
268:15 271:8	four	funny	266:10 267:10	17:6
274:11 279:10	15:5 79:3	142:7	270:7 276:18	gleaned

118:20	210:4 211:13	242:3 268:22	234:13 237:18	263:19 264:4
go	218:25 223:11,25	greater	273:19 307:13,17	266:23 267:11
40:11 43:9 46:15	230:8,17 237:11	64:1 102:8 114:17	hand-selected	285:1,4 305:16
62:9 99:3 113:17	237:14 241:2	155:12 240:12	68:4	306:21 311:18,22
114:5 116:18	245:17 247:11	247:12 262:24	handed	311:25 312:1,3,14
135:11 141:7	248:24 249:24	263:7 267:12	14:25 15:14 20:3	health-related
146:16 157:5	259:5,7,13 263:4	268:2,7,24	33:7 36:11 153:16	25:20
188:6 204:9 215:5	263:5 265:1	ground	165:14	healthcare
217:15 218:4	273:15,19 278:2	13:23 282:7	handful	32:11 127:6
219:16 234:2	280:10 282:6,23	grounded	104:13 177:8	hear
241:3 245:12	283:1,16 284:4	281:15	294:21 314:25	294:17
250:4 253:24	286:4 288:8,20	group	handing	heard
254:6 256:24	289:20 294:2,11	92:12 97:4 188:4	37:14 77:1 84:22	223:2,12 281:2
261:21 264:2	302:16 307:13	190:17,20 236:21	136:10 149:25	heavily
269:8 274:3 275:9	308:14 309:23	278:25	173:11 175:21	145:2
277:25 280:8	315:6 316:14	groups	180:9	heavy
282:8 284:11	317:6	262:14	handle	92:18 119:10 120:3
289:2 309:21	GOLKOW	grow	20:15 78:10	120:18,24 121:2,9
315:4,5	1:24	102:21	handwriting	121:15 123:8,12
go-to	Gonzalez	growing	18:3	126:1 296:16,21
288:13,21	186:20 187:14	178:12	handy	297:13,25
goes	199:24 270:20	guess	90:8	help
78:25 79:8 92:22	271:2	117:7 128:23	happen	35:1,6 100:11
162:2 239:20	good	140:20	198:3	236:3
278:15	9:8,9 52:11 100:19	guidelines	happy	helps
going	100:20 165:4	246:4	14:8	215:1
15:2,6 17:18 20:7	190:24 211:9	gynecologic	hard	hesitant
21:15 22:11 32:19	280:18 308:18	20:20 147:17	40:9	223:7
32:20 33:21 34:9	310:5,6	149:16 290:3	hard-pressed	heterogeneity
35:10,19 36:24	GORDON	Gynecology	178:13	169:20 170:22
37:2,9 41:14 45:4	3:3	147:21	HARDY	171:10 172:14
45:7 49:9 52:12	gotten	H	2:17	195:13 213:11
52:15 54:23,25	151:17 222:23	H	hazard	215:19,24 228:7
61:8 65:1 66:17	grab	6:12	266:12	228:13,18 230:20
76:8 78:4,5 86:23	164:5	habit	head	231:11 269:7,14
91:14 107:21	grabbed	115:9	89:6 103:16 246:11	271:1
115:2 116:20	162:13	half	252:21 253:8	heterogeneous
139:6 149:21	grabbing	268:1,2	290:2	196:2,4,5
150:16 151:9	162:11,12	halfway	health	Hey
163:23 164:4,20	grant	39:1 212:20 260:23	6:4 76:3 86:13,16	116:14
164:25 165:8	5:19 283:18	hand	105:3 145:16,19	Hi
169:2 171:19	graphic	15:6 18:1,1 32:19	145:23 146:3,8	294:17
172:1,3,11 173:8	301:18	36:24 45:4 54:23	147:6 150:17	hierarchy
175:16 180:5	graphics	77:4 139:7 151:9	151:11 166:12,24	158:24 300:12,17
182:1,2 200:11	301:19,21	164:25 202:14	186:22,23 188:19	301:17
202:14 204:24	great	212:15 227:5	196:14 253:14	high
209:11,12,14	14:15 38:2 52:23		261:8,17,18,24	130:11,16 261:25

higher 113:23 114:8 134:24 181:23,24 229:5 230:9,17 231:13,21 232:14 240:20 263:4 272:19 304:25	202:13 263:18 264:4,15,17 267:9	IARC's 93:8 103:7 109:14 306:25	Imerys's 282:2	152:1 155:21,25 156:3,5,6 293:3
highest 274:9,12	hour 14:18 52:12 113:7 209:13 259:6,8	idea 46:7	immune 25:23	inadvertent 220:12
highlighting 50:2,4,7	hours 71:25 72:12	ideas 225:23,24	impact 227:2 261:8,19,24 316:22	Incessant 40:19
highlights 238:9	Houston 2:18	identification 13:12 15:3 17:20 20:9 32:22 35:21 36:22 37:13 41:17 45:8 49:12 61:17 77:2 84:20 91:17 107:23 136:11 139:8 149:24 151:13 165:2 169:3 173:10 175:19 180:7 202:15 205:2 227:6 234:11 237:19 273:17 307:15	impacting 238:18	incidence 93:5 111:23 112:10 112:18 113:23 304:19 305:12
Hill 111:8,11 141:3 144:25 182:21 183:8 244:3,20 246:3 247:15 248:24 249:15 258:23 263:9 292:3,8,17 308:12 308:20 309:5,14 313:14	Human 5:10	identified 13:19 25:10 29:11 29:17 41:2 49:8 49:16 58:5,16 59:5,15 60:8 66:23 70:19 122:24 123:19 134:17 253:20 254:14 255:14	implies 138:1	include 21:8 29:25 42:12 46:16 47:12 115:8 118:10,14 123:3,7 162:16 175:11 187:24 188:9 193:9,19 217:4 240:14 271:17 278:22 311:12
histologic 187:5	Huncharek 6:16 175:13,17 176:24 177:9	identify 28:20 29:12 40:5 221:25 224:8 257:22	importance 113:3 197:22 199:15 200:18 201:1,13 202:10 204:13 205:25 206:4	included 20:24 26:14 29:9 42:16 43:15 131:7 137:1 139:4 140:17 161:6 188:19 193:24 212:24 278:14 284:13 286:22
histology 35:5	hundred 104:10	identifying 146:8	important 22:3,6,8 56:14,15 71:12 81:3,4 134:25 140:21 142:8 149:20 158:10 164:14 198:3 219:15 227:2 239:10 245:2,5 250:22,25 299:24	includes 29:23 50:1 196:16 284:25 311:2
history 76:6 218:18 222:21 222:22 224:2	husband 282:22	Illinois 3:19	impossible 102:18 178:19,20	including 51:18 63:4 69:2 116:6 167:7 170:22 184:9 190:18 240:21 268:9
hold 86:25 87:3 122:12 123:22 124:22 125:25 295:10 302:25 303:18	hypotheses 224:10,16,24 225:2 225:14	illustrate 144:24	imprecise 250:14,15	inconsistencies 271:20 272:5
hope 27:1 285:12	hypothesis 40:20 149:10 189:16	imagine 209:8 288:25	impression 68:14 144:15,19 222:23	inconsistency 271:23 293:1
hopes 27:14 31:5	I	Imerys 3:2 8:13,15 280:16 280:21,24 281:7 281:11,19,25	improved 239:16	inconsistent 154:12
hoping 242:16	IARC 5:8 89:14,20,22 90:4,14,17 91:6 92:11,22 93:13,24 94:8,20 95:6 96:2 96:9,21,25 97:12 97:20 98:8,16 99:11,20,20 100:22 101:1,2,17 101:20 103:2,13 106:19 108:20 109:4 110:24 122:18 123:1,3,7 146:13 147:12 152:23 252:6,12 252:15,20,23,25 258:9,11 293:20 293:23 314:6,9,12 315:14		in-depth 182:19	incorrect 210:3
hopping 282:6			inaccuracies 160:5 220:12	increase
Hotel 1:17			inaccurate 203:13 218:12 220:23,24 221:1,2 276:8	
Houghton 6:22 186:21,22			inadequate	

131:20 224:25 275:24 276:2 278:9 increased 105:15 112:10,18 125:6,23 134:14 147:25 148:21,21 149:3,3 155:4 163:11 166:7 167:5 176:15 181:15,24 185:3 187:6 225:8 226:23 247:21,22 248:6 249:13 250:1 256:12 262:24 313:11 increases 93:4 94:3 203:20 increasing 276:20 277:10 278:10,20 independent 120:16 122:12 123:22 INDEX 4:1,8 5:1 6:1 7:1 indicate 70:18 186:25 220:22,24 indicated 33:20 57:4 82:20 166:24 197:17 236:25 298:12 301:4 312:4 indicates 307:24 indicating 102:5,6 120:25 121:2 215:10 individual 25:19 198:18 199:9 215:11,15 290:20 301:7 302:4 individuals 12:10 158:14 induced 223:2	inevitable 230:16 inevitably 226:12 230:8 infertility 28:12,22,23 29:14 29:16 286:14 influence 265:20 inform 42:21 165:23 179:15 180:12 206:17 information 56:19 57:17 76:25 82:18 88:18 98:2 111:3 118:18,20 118:23 119:3 121:10,23 122:8 147:23 149:8,20 190:9 208:9 220:2 293:14 Ingham 10:2 11:10,21 13:23 15:10,20 16:11,18 17:7,14 17:18 18:13,17,24 19:1,8 25:25 31:2 31:4,7 32:11 45:6 45:18 47:2 48:9 48:20 50:6 51:6 51:22 54:20,24 61:9,25 74:18 115:19,20 116:10 119:17 295:12 ingredients 123:23 126:2 inhalation 303:17,19,24 inhaled 142:6 304:1,4,9 inherent 220:17 initial 52:3 initially 220:5	Initiative 186:23 285:4 insignificant 267:15 instance 127:25 257:25 Institute 6:3 7:3 150:23 209:9 283:19 insufficient 174:9 178:6 Intellectual 44:18 intend 26:13 37:18 41:1 76:4 86:20 250:4 294:7 intense 185:8 intent 59:12,18 60:16 161:4 215:9 256:15 285:9 intention 59:8 60:13 291:15 interest 23:8 221:25 interested 44:19 68:18 149:15 261:18 284:23 320:16 interesting 68:23 154:2 internal 127:12,13 International 7:16 internet 30:16 interpret 181:5 interpretation 163:15 169:22 170:12,25 195:15 198:15 269:16 interrupt 113:6,8 116:16	intertwined 244:12,21 interval 134:20 137:17 265:10,13 interventions 7:8 227:9 229:7,13 interview 132:2 225:22 235:5 235:8,12 interviewed 132:10 239:18 240:21 interviewees 235:22,23 236:4,5 interviewers 222:19 223:3,13 224:11,17,24 225:3 interviews 30:24 225:11 introduce 8:6 invasive 6:14 139:18 185:14 187:1,7 193:5 264:10 invested 209:9 investigation 286:3,22 investigators 188:8 204:17 206:5 238:20 262:12 invite 225:4 invoiced 14:19 invoices 4:10 15:1,5,7,14,15 15:23 16:8,12,15 16:17,20 33:18 invoked 213:10 215:18 involve 199:20 involved	13:7 88:9,19 112:6 180:21 280:23 281:5 285:8 involvement 21:9,20 22:13 27:20 283:2 285:17 291:25 involves 284:8 isolated 236:20 isolation 297:5,9,13 issue 22:5 57:12 59:1,9 67:11 68:12 81:5 84:7 85:25 88:21 94:20 107:4,19 109:19 110:21 126:22 128:22 144:16 149:17 160:20 163:5 166:2 174:1 188:14 190:13 197:22 212:9 213:21 214:11 216:1 219:7 221:4 233:23 240:10 242:3 253:11 315:19 issued 51:2 149:22 issues 26:5 192:5 206:20 284:18 item 21:3 39:25 items 39:21 40:5,15,23 40:23 42:12 46:12 46:18,23 48:19,21 49:2 50:5,11 306:21 308:24 <hr/> J <hr/> J 5:19
---	---	--	---	---

J&J 9:12 310:8	99:16,24 100:2,8 100:13,19,21	201:6,20 202:12 202:17 204:18,24	jessica.brennan... 2:24	188:8 198:12 208:14 222:17 252:16
J.M 2:14	101:5 102:9 103:1 104:20 105:6	205:3 206:7,15 207:5 208:17	jfoster@gordonr... 3:5	judgments 184:7
Jack 44:6	106:1 107:10,21 107:24 108:12	209:17,20,22 211:9,12,18	JNCI 6:21	jumbled 106:2
James 2:19 3:20 4:3 8:9,9 8:19 9:7,10 13:1,6 15:4 16:3,7 17:21 20:10,14 21:1 22:22 23:13 24:24 25:3 27:2,19 29:15,21 32:23 33:3,5 34:3,7,9,13 34:14 35:10,18,22 36:4,9,14,23 37:23 38:5,6 41:13,18,24 42:3 42:4,10,23 45:9 46:2,10,19 47:22 48:7 49:1,9,13,16 49:19,23 50:16,23 52:13,20 54:19 55:1,7,10,13 56:1 57:22,24 58:7,9 58:18 59:17 60:22 61:7,13,18 62:15 63:1,8,18 64:13 65:10,16 66:4 67:1,10 68:9 69:12 70:20 71:24 72:20 73:1,11,15 73:16 74:4,13 75:3 76:11,24 77:3,8,11 78:6,11 78:16 79:6 81:1 81:16 82:1,9,24 83:16 84:1,13,15 84:18,21 85:1 86:8,17,19 87:19 88:20 89:8,18 90:3 91:9,18,20 91:24 93:18,23 95:1,13,15 96:8 96:15,19 97:17 98:6,15,23 99:4,9	109:8,17 110:17 111:6 112:16 113:9,12,20 114:2 114:23 115:7,16 116:7 117:1 118:9 118:21 119:4 120:1 121:7 122:9 122:20 123:13 124:4,10,13 125:9 125:24 126:7 127:19 128:1 129:12 131:1,18 132:12 133:8,14 135:3,10 136:6,20 137:11 139:5,9 142:19 143:17 144:3,8 145:3,18 148:19 149:14,21 149:25 150:2 151:15 152:12 153:9 157:21 160:14 161:8 162:9,17,24 163:20 164:20,25 165:3,6,13 167:13 168:15,25 169:4 170:6 171:15,18 171:20,22 172:1,6 173:8,11,14,16 174:22 175:2,12 175:16,20 176:8 177:7,17 178:21 179:13,24 180:5,8 180:10 181:6 182:17 184:15,23 186:9 188:23 189:21 190:3,11 191:1 192:18 193:4 194:1,7,17 196:1,15,19 198:5 199:10 200:10,24	213:24 214:7 218:24 219:2,16 219:19,24 227:4,7 229:9,23 230:23 234:8,12,14,21 236:14 237:20 242:6,10 243:1 246:7,23 247:6 248:1,7,15 251:1 251:8 256:1 258:3 259:4,9,18 266:17 267:13 268:8,17 271:15 273:15,18 274:14 275:18 277:2,25 279:7,11 280:2,6 282:7,15 287:5 292:20 302:14,23 304:16 306:1,15 307:8,12 307:16 308:4,10 308:19 309:9,18 310:10 312:6 314:25 315:2,3,13 315:24 316:19 317:1	job 287:1 Joellen 7:12 Johnson 1:5,5 2:16,16 8:9 8:10,12,12 9:6,6 70:21,25 71:3,9,9 73:22,22 75:8,8 75:15,15 79:20,20 79:24,24 80:2,2,4 80:4,6,7,16,16 83:1,1,8,8 118:23 118:23 121:11,11 121:19,19 124:20 124:20 281:8,8,19 281:19 302:22,22 315:12,12 Johnson's 70:21,25 71:3 80:10 Jonathan 3:9 8:15 journal 5:11,14 6:18 7:3,10 7:13,16 21:24 22:14,16 23:10 28:4,4 65:14 148:7 166:12,24 243:21 journal's 22:1,9 journals 147:22 judge 223:25 judged 184:13 252:23,25 judgment 156:7 175:8 176:24 181:1 182:23	kindly 36:16
<hr/>				
K				
<hr/>				
K 7:18 Kadry 7:21 Kat 31:16 Kathryn 6:20 keep 49:19 209:14 247:20 249:24 keeping 36:25 Kemble 3:8 Ken 288:15 Kessler 44:5 290:1 kind 33:1 35:2,6 40:9,18 154:2 159:1,6 182:14 211:5 220:17 222:22 223:20 229:1 240:12 253:16 264:12 270:21 292:3 293:1,10				

knee-jerk 231:19	242:2 248:21 252:19 253:14	129:11 130:21 140:22 146:6,7	288:3 293:10 294:2	106:18 107:17 160:16 172:17
knew 80:18 289:21	261:17 263:14 276:5,12 279:2	164:7,10 Lanza	left-hand 167:17 203:3	212:13 limitations
know 11:12,13 12:4	280:24 282:1,5,8 282:10 285:19,22	7:9 226:8,10,17 227:4,8,12,12	210:13 lesser	103:24 104:3 191:5
13:24 14:7 16:17	286:9 287:2 288:4 289:25 290:5,18	230:2,24 232:1,4 large	113:3 let's	200:8 301:7
23:6 24:10,14	290:19,20 293:15 296:13 297:16	29:8 30:2 46:3 47:14 79:25	11:7 19:13 99:24 100:2 113:11	limited 79:2 130:8 163:21
31:22 34:6 35:4	298:8 305:9 306:9 knowing	143:25 200:6,6 205:21	153:12 170:19 172:9 194:18	201:10 205:11
37:25 40:8,9,10	68:18 95:9 206:13 knowledge	largely 225:25 311:15	218:16 221:22 237:12 240:5,17	233:19 294:2
40:11 41:11 42:20	11:22 17:1 41:9 43:10 47:11 82:25	LAW 2:7	253:23 264:14 275:22 277:25	297:14,14
44:7 45:17 46:15	121:18 130:22 181:11 226:6	lawsuit 239:14	288:15 299:2 letter	line 61:24 113:13
46:17 47:9,14	243:23 248:20 281:18,22 314:12	lay 232:25 256:8	5:7 84:2,6,23 85:3 85:3,11,22	209:17 319:5
49:6 50:18 51:6,7	known 224:10,16 225:15	layman's 229:16	letters 32:15	linear 275:13,24 276:2
51:8,11 54:14	225:19,19 knows	lead 48:15 102:1 121:6	level 39:14 45:1 76:1,1	lines 55:10 61:20,21
57:6 59:11 62:11	223:11 290:20 <hr/> L <hr/>	171:13 226:12,23 230:8 232:14	102:1 105:21 106:4 157:9	240:7
64:24 68:13 70:23	L 2:23 6:20	292:12 leading	181:23,25 253:24 254:16 255:23	link 88:25 89:10 168:4
71:2,5,9 72:4,7,11	L.L.P 2:17	147:21 149:16 182:22	263:5 270:24 300:5	168:13,17
74:6 75:1 76:22	label 97:3,7	leads 125:8 231:20	levels 44:3 75:24 105:16	list 5:3 26:14 27:16
78:25 79:8 80:3	labeled 130:4 140:7	learn 44:19	121:24 122:3 190:19	33:15,19 38:21,25
80:16,19 83:8,14	laboratory 57:5 89:24 106:24	leave 78:5	LHG 1:7 319:4	39:8,9,10,18,22
83:20,24 84:6	lack 191:3 192:6 215:10	leaves 155:20	LIABILITY 1:7	40:6,15,15,22
86:3,4,7 89:13	ladies 69:25 311:4 312:23	lectures 30:21 158:23	life 25:20 208:7,8	41:3,4,11,15,22
95:5,8 96:12	Langseth 6:12 173:4,9,17,18	led 125:23 160:11	lifetime 272:20 276:21	41:24 42:1,5,5,11
101:24,24,25	175:7 177:19 178:23 209:24	240:12,13,20 266:16	277:11,19 light	42:11,15,24 43:23
102:4 103:15,17	210:2,9,24 language	left 66:18 139:22 140:6	95:10 limitation	44:24 45:6,10,12
104:14 106:11,12		167:23 275:1	104:7,17,22 105:1	45:15,17,18,19,20
108:10 112:17				46:6,22,23 47:7
114:11,12,12				48:20,20 49:11
123:17 124:17,19				51:6,9 80:10
129:23 131:25				246:17,18 290:25
136:2,4 143:3,7				306:18
143:21 148:16				listed
149:2,15,20				41:10 43:19,23
152:19 157:11				46:12,13 140:7
159:4 160:23				151:25 154:6
163:11,12 178:14				194:25 252:2
181:10 183:20,24				286:10 301:22
184:8 186:4				listing
188:12 190:22				286:18
193:17 200:6				lists
207:3 208:21				46:20 50:11
209:15 217:3,12				
217:13,23 222:21				
223:5 225:6,23				
232:10,13 239:4				
239:21 241:24				

literature 5:12 45:3 47:3 51:22 52:9 56:12 56:22,25 58:1,11 58:22 60:13,19 62:21 63:10 64:1 64:3,7,18 65:2,5,8 65:9,12 66:15,21 66:23 67:5 68:2 72:9 75:4,7 78:25 81:19,25 82:3,12 88:6 89:4,9 102:11,20 103:19 103:21,25 104:22 105:7,14,17 106:19 107:5,14 107:18,20 111:8 111:15,22 112:17 119:9 120:17 126:12,14 129:9 131:6 156:16,19 157:7,8,10,14 161:12 162:7 163:7 166:10 182:10 197:21 198:1,1 199:11,14 200:16,25 201:12 202:4 212:10 224:19 226:5 227:15,20,21 229:15,25 231:3,6 242:8 245:11,21 246:9,25 247:8 253:21 254:7,10 254:13 255:2,4,9 257:25 260:4,12 262:3 263:18 266:21 271:17 272:6 287:7 291:20 292:2 295:2 296:2,3 304:22,23 309:1,7 309:8 311:1 litigation 1:7,24 11:8,9 13:19 16:9,13,16,24 17:4 21:9,21 22:6	22:14 27:21 28:2 30:7,18 31:8,18 32:5,8,13 44:13 47:17 67:3 68:19 73:2,7,22 74:1,2 74:15,22 87:15 88:9,19 97:19 110:6 118:11,15 118:24 121:11 124:15 126:18 127:20 131:3 150:22 153:5 174:23 185:10 214:3 233:15,19 234:1 236:16 254:20 255:5,9 271:5 280:24 281:5 285:18 290:8,12 292:6 294:5,7 295:11 319:2 little 11:11 12:1,4 27:10 59:4,14 138:14 154:22 155:20 161:17 267:23 288:19 289:5 311:17 lives 300:9 LLC 2:7 LLP 2:3,21 3:3,7,13,18 loathe 166:14 locations 262:13 lodged 36:12,13 long 26:14 27:16 220:11 259:4 267:14 280:18 291:24 310:9 314:24 315:5 longer	46:6 190:7,22 194:10 237:5 Longo 73:12,14,17 118:10 118:10 Longo's 73:19,23 74:19,22 look 19:23 29:6 35:4 40:12 45:10 61:19 61:20 63:23 70:4 70:4 77:16 80:9 89:19,23 92:7 104:2 105:3 108:13 109:23 112:2 126:12 128:17,19 132:6 138:13 139:12,15 139:22 140:24 144:25 145:1 150:22 155:5,10 155:13 156:11 161:19 164:4,9 167:15 169:1,15 180:14 184:7,12 184:24 186:25 195:9,11 197:25 199:8 203:2,15 208:6 219:8 229:10 235:2,4 237:21 238:6 262:21,21 263:1 263:17 264:17 267:21,24 268:5 269:11 270:2,3,19 270:20 272:24 274:3,25 276:14 276:15 278:24,24 279:17 301:6,6 303:6 looked 21:25 23:4 35:3 43:12 44:3,9 62:12,13 63:22,25 73:2,20 84:12 85:25 89:13,14,15 89:25,25 104:11	106:19 111:22 112:20 113:2 120:23 127:13,22 128:21 129:4 131:10 135:24 142:5 147:16 153:25 154:11,22 156:21 179:15 188:1 193:23 194:9 197:21 199:12 200:17 206:17,17 207:12 209:5 213:17 226:20 229:7 237:12 240:1 253:10 269:20 273:4,22 274:18 292:21 303:4,10 304:4,14 312:13 313:4 looking 19:24 20:5 21:3 22:22 25:19,23 27:4 28:11 42:5 44:11 55:7,10 67:24 89:10 90:11 95:17,23 104:8 128:8 130:14 131:7 132:13,14 137:4 155:7 156:2 157:2 167:2 188:14 191:15,19 191:24 200:8 212:9 226:19 227:12,18 232:1 235:2 236:2 244:25 260:17 264:19 273:25 274:7 278:22 looks 36:25 105:8 128:24 140:9 151:19 Los 285:4 lot 30:2 86:15 154:25 174:13 222:20	223:22 224:24 282:6,7 lots 40:10 low 75:24 190:19 213:9 215:17 228:8 low-level 208:19,22 209:11 lower 134:24 236:17 263:5 304:18 305:12 lower-level 288:20 lung 141:12,13,23,24 142:3 143:10,14 143:21 144:17 145:5 245:9 247:19 249:1 259:24 260:7 Lynn 29:25 <hr/> M <hr/> M 7:4,12 M.S.P.H 1:12 4:14,21 5:5 9:2 318:2 319:3 magnitude 245:8,14 246:14 249:1 251:23 253:6,12,18 256:4 256:6,25 257:12 257:14,18,24 258:7,13,21,25 main 19:17 35:3 44:18 maintain 299:21 major 57:7 239:5 292:14 majority 49:2 104:10 130:24 233:10 272:18
---	--	---	---	--

273:8,22 276:9 303:4,7,8 making 66:9 69:15 71:13 100:13 142:1 159:1 182:22 198:12 229:6,22 247:20 298:6 299:24 male 113:1 males 112:5 man 123:17 manner 254:18 255:3 manufacturing 83:2 manuscript 302:10 March 4:24 5:5 10:6,9 17:7 19:8 30:22 45:13 46:13 47:1 47:17,24 48:5,19 49:3 50:18 51:11 56:2 mark 15:2 17:18 20:7 32:20 35:10,14,19 37:9 41:14 45:7 49:9 61:15 91:14 107:21 149:21 164:20 169:2 173:8 175:16 180:5 204:24 234:6,8 237:14 273:15 307:14 marked 4:9 5:2 6:2 7:2 15:3 17:20 20:9 32:22 35:21 36:17,22 37:13 41:17 45:8 49:12 61:17 77:2 84:20 91:17 107:23 136:11	139:5,8 149:24 151:13 165:2,3,18 169:3 173:10 175:19 180:7 194:20 202:13,15 205:2 212:16 227:4,6 234:11 237:19 273:17 291:1 307:15 market 113:22 122:5 marketed 79:13 85:16 88:14 MARKETING 1:6 marking 61:11 76:24 136:7 material 49:18 77:25 materials 4:17,22,24 5:3 33:23,24 34:16,22 35:25 39:2,8,12 39:22 40:6,15,22 41:1,3,16 42:1,15 42:24 43:15 45:5 45:19 47:8,15,23 47:25,25 48:9 49:10 51:2,10 72:1 117:23 118:7 120:17 121:10 306:17,18 materials-consid... 246:18 matter 9:12 matters 13:20 McTiernan 44:4 290:21 MDL 1:6 5:3 10:24 11:3 11:6,21,25 12:2,7 12:17,20 13:16 14:17,19,21 15:1 15:8,11,16,21 16:10 30:14 32:17	33:20 34:23 37:5 37:6,15,19 42:13 42:16 43:16 44:24 45:20 46:5,12,21 47:8,24 48:10,20 49:3,11 50:6,11 51:1,3,6,10,23 57:8 74:1,16 79:17,19 88:2 97:19 115:8,13,25 116:8 119:14 123:14 131:2 160:15 164:6 170:1 171:5 172:20 176:23 197:21 271:4 294:5 319:2 mean 32:4 34:19 40:8,16 41:6 100:16 113:13 142:18 143:20 145:12 229:19 230:24 232:4 248:18 287:23 288:5 310:22 measure 106:25 299:14 300:6 measures 300:4 measuring 274:16 277:19 mechanism 57:1,13 63:4 87:11 88:16 181:12 182:6 183:10 254:13,15 mechanisms 48:14 57:2 83:21 mechanistic 60:7 260:15 media 185:8 232:21 233:1 233:3,6,18,22,25 238:13,18 240:22 medical	28:24,25 56:11 102:11 141:22 144:16 145:4,8,9 145:13 146:10,25 147:16 148:14 150:10,18 156:16 156:22 157:14 253:21 255:2 medicine 159:4,5 medroxyprogest... 154:7 meet 12:7,9 39:14 meeting 9:11 Melville 2:13 members 293:17 memories 239:15 memory 239:21 240:12 menstrual 222:21 224:2 mention 36:15 81:4 118:12 123:12 191:5 mentioned 12:19 19:18 26:21 26:24 28:21 31:12 31:14,17 147:4,5 154:5 164:22 212:12 283:23 285:24 286:9,13 292:25 297:25 316:21 mentioning 148:20 mesothelioma 112:11 114:9,11,18 met 12:10,14 123:17 245:10,21 246:6 262:3,4,19 271:14 280:18 314:13	meta-analyses 7:7 89:4,14 137:2 154:23,24,25 155:10 158:2,9,19 158:25 159:6,8,11 159:17,20,22 160:2,5,10,16,19 160:24,24 161:3,7 161:9,11,15,21 162:8,10,13,19 163:1,3,14 164:8 164:15,17 165:23 166:2 167:8 170:2 173:3,5 175:14,17 177:9,10,12,19 184:1,7 193:18,23 195:21,22 199:13 206:16 207:6 210:10,12 212:25 213:7,19 216:17 226:20 227:3 228:18,24 235:15 241:12 260:18 262:21 267:25 268:6 300:16 301:16 309:1 312:25 313:3,7,10 meta-analysis 5:12 6:7,10,15 7:20 108:1 110:9 147:24 159:13 164:21 168:25 169:1 171:6 175:22,25 177:3 183:14 184:6,14 187:22 206:24 207:11 213:4 216:18,22 241:17 254:3 272:1 312:19 Meta-Epidemiol... 7:8 metal 122:24 metals 5:9 119:10 120:3 120:18,24 121:2,9
---	---	--	---	---

121:15 122:16 123:4,8,12 126:2 296:17,22 297:13 297:25 method 242:11 293:10 313:18,18 methodologically 205:24 methodologies 290:16,23 methodology 155:18 157:19 184:22 293:10 309:11 313:18,21 methods 53:14 59:7 197:15 205:8 225:16 293:15 313:25 Michael 6:16 44:6 Michele 21:13 31:12 Michelle 2:5 8:24 12:11 14:6 15:23 20:10 22:23 24:24 32:23 34:3 35:10 37:24 49:20 73:15 78:6 280:2 307:12 middle 92:8 132:14 171:21 233:7 240:25 midway 238:3 migration 59:1,3,9,16 miked 18:2 millers 111:16,19,23 112:4 112:12,19 Mills 7:18 25:22 273:9 273:16 mind 36:5 48:18 101:7	104:6 110:22 152:7 243:7 245:6 256:21 268:13 282:20 288:1,9 299:5 316:25 mine 33:1 mineral 53:14,17 mineralogist 65:23 82:21 miners 111:16,19,23 112:3 112:4,11,18 mines 281:7,19 mining 54:2 281:25 282:1 282:4 minute 163:5 308:13,16 minutes 40:12 113:7,18 288:3 302:15 misclassification 106:20,22 107:2,4 107:9,12,16,17 110:1,13,22 111:4 242:19 misleading 113:14 161:17 misrepresented 99:2 misstate 98:23 misstates 61:1 69:20,24 98:9 98:19 119:19 199:16 208:3 271:10 298:3 307:3 misstating 99:16,21 101:9 279:5 mistaken 80:7 286:24 mistakenly	199:19 200:5 misunderstanding 249:4 mixture 40:23 Mizgala 3:20 8:19,19 99:22 100:1 Mm-hmm 50:8 140:23 153:17 183:16 moderate 181:14 248:23 250:15 287:18 Modern 288:15 modest 247:9,23 248:4,9 248:10,22 249:7 249:11 250:10,14 250:18,21 287:11 287:17 288:23 modifiable 182:25 Mohamed 7:21 molecular 25:23 moment 19:22 132:6 163:19 173:20 215:6 239:2 277:23 298:14 money 209:10 monograph 89:20,23 90:5 91:16,19,22 94:6 94:9,18 95:17,21 95:21 96:10,14 101:14 123:1,3,7 123:12 314:9,19 315:15 Monographs 5:8 months 270:24	Moorman 1:12 4:10,12,14,15 4:19,21,23,24 5:5 5:16 8:5 9:2,8,17 19:24 21:5 33:3,6 34:15 35:17,23 36:20,24 37:4 38:20 41:16,20 42:2,5 45:4 49:14 49:24 52:21,23 55:14 56:6,8 57:25 60:10 61:3 61:8,14,19 64:14 67:12 69:22 74:3 77:1,12 78:17 80:11 84:2,22 85:2,4 90:8 91:5 91:11 92:1,5 94:6 95:16 107:25 108:14 115:8 117:2 119:11 128:3,16 130:15 136:6 139:10 140:19 144:9 150:3 151:9,22 153:10 157:22 165:14,22 167:16 171:16 172:12 175:13,21 180:11 184:24 195:12 196:20 200:11 201:9 202:18 209:23 211:19 218:24 219:25 234:16 235:4 237:21 240:4 244:1 245:25 251:15 257:10 259:19 260:20 262:2 264:17,25 269:11 273:12 274:8 280:1,18 294:17 296:5 301:15 302:6,12 302:24 304:17 307:18 308:11 309:18 310:5,9	313:17 314:22,25 315:14 317:6 318:2 319:3 morning 9:8,9 14:25 20:3 28:8 33:17 36:10 164:22 280:19 282:15 294:19 Morristown 3:8 mortality 90:21 92:17 93:5 Mount 3:8 move 69:10 99:24 100:2 232:18 moved 165:16,21 Moving 262:2 mparfitt@ashcr... 2:5 mucinous 303:12 316:3 MUELLER 2:7 multicenter 29:8,24 Multiethnic 285:2 multiple 11:12,12 24:4 71:19 96:25 140:18 158:23,25 161:15 256:13 258:24 264:3 312:25 mutagenicity 53:8 <hr/> N <hr/> N 2:1 3:1 8:1 N.W 3:13 name
--	---	--	--	---

9:10,15,17 10:3 12:12 19:20 280:19 319:2,3 names 12:24 75:11 290:1 290:19 NAPOLI 2:12 Narod 211:24 212:1,5 214:23 215:3 216:2 National 6:3 7:3 150:23 209:9 283:19 nature 200:12 203:5 211:1 NCI 151:5,10,24 152:25 156:1,9 157:11 292:21 293:1,9,17 NCI's 155:23 nearly 268:6,23 necessarily 60:8 69:18 70:8 104:25 181:5 182:16 194:11 211:7 232:15 252:16 necessary 309:10 need 14:7 18:23 32:23 37:24 52:5 69:18 70:4,8 113:10 219:8 231:3 249:18 273:13 needed 180:18 181:9 needing 39:14 neither 136:14 320:12 never 23:7 82:2 123:17	138:4 157:3 188:5 218:23 220:16 222:23 223:12 225:18,19 274:21 never-use 265:5 Nevertheless 204:12 new 1:2 2:13,22 3:8 10:23 46:12,17 47:10,15 48:8 50:10,17 51:5,7,8 51:16 115:13,24 117:19 118:2 119:16 147:23 148:10 225:24 284:3 285:9,25 newly 26:10 NHS 188:12,14,24 189:7 189:12,14 191:7 191:23 192:22 205:4 216:9 nickel 119:12,15 122:21 nine 29:3 240:7 non-mucinous 278:12 non-occupational 93:25 non-serous 310:25 non-statistically 134:12 236:22 non-talc 131:8 non-users 278:13,23,25 279:18 nonresponsive 57:23 58:7 69:11 86:17 95:14 144:3 171:23 200:12 219:1	nonresponsiveness 64:16 nonsignificant 93:3 94:2 nonstatistically 94:1 North 1:18 135:18 137:1 138:17,20 139:3 140:16 285:16 292:13 320:1 notable 301:9 Notary 320:3,23 note 74:14 93:19 94:2 140:25 141:10 172:20 203:16 207:12 227:25 228:18 278:16 notebook 34:24 noted 15:24 92:12 166:13 177:19,21,24 178:25 194:11 212:23 272:1 notes 34:8,21 35:1,24 280:3 notice 4:15,19 32:20 33:7 33:13 34:1,5 noticeable 301:13 noticed 290:24 notices 33:11 noting 174:12 180:24 null 134:9 137:8 265:14 number 4:9 5:2 6:2 7:2 21:3 46:3,17 47:14,14	79:5 89:5 90:9 104:12 107:15 120:14 128:21 155:5 200:1 206:16 210:2 212:13 246:16 251:15 272:17 276:20 277:10 278:10,21 284:21 287:19 295:22 319:4 320:23 numbers 180:9 numerical 289:2 numerous 187:15 245:13 314:5 Nurses' 186:23 188:18 196:14 263:19 264:3 266:23 267:11 <hr/> O <hr/> O 8:1 object 26:23 57:22 58:7 64:15 66:17 80:23 86:17 88:4 95:13 101:10 144:3 166:21 171:22 172:8 200:11,21 218:25 247:3 objection 12:21 22:20 27:7 41:5 42:8,18 45:23 46:8,14 47:19 48:3,22 49:5 50:12,19 51:24 54:10 55:20 57:14 58:3,13 59:10 60:14 61:1 62:8 63:6,12 64:5 65:6,15,19 67:6 68:6,22 69:20	71:15 72:17,24 73:8,24 74:10,25 76:7 78:20 81:6 81:20 82:5,19 83:12,22 84:9 86:2 87:16 89:2 89:12,21 91:7 93:16,21 94:22 95:3 96:5 97:14 97:21 98:9,19 99:3 101:3,21 102:16 104:1,24 105:24 107:7 108:9 109:5,16 110:7,25 112:13 113:25 114:20 115:15 116:1,13 118:1,16 119:1,19 120:20 122:6,14 123:10,25 124:25 125:17 126:3 127:17,23 129:6 130:18 131:14 132:4 133:5,11 134:18 135:6 137:9 142:16 143:16 144:20 145:11 148:15 149:11,18 152:11 153:6 157:17 160:7 161:2,18 162:14,21 163:17 167:10 168:11 170:4 171:7 172:22 174:19,25 175:9 176:6 177:1 177:14 178:9 179:9,23 180:2 181:3 182:13 184:4,18 188:16 189:17,25 190:6 190:15 192:16,25 193:14 194:5,14 195:24 196:12,17 197:23 199:2,16 201:3,15 204:15 204:22 206:2,12
--	---	--	--	---

207:1 208:3	106:16	165:21 210:4	181:7 185:19,24	188:5 238:12
213:22 214:4	occur	308:17 315:3	185:25 186:16	246:1,13 247:10
228:15 229:18	242:19	okay	187:3,10 191:22	248:20 249:21
230:4 236:11	occurred	12:9 13:2,13,14,22	192:4 194:19,23	oncologist
241:15 242:9,14	220:11,19 233:14	14:1,2,8,9,13,14	195:3,6 200:11,15	290:3
245:23 246:20	occurring	14:22 15:13,22	203:2 204:4	oncology
247:24 248:11	115:9	16:22 17:19 18:3	207:10,16 209:18	147:17 149:17
250:23 251:4	OCWAA	19:13 20:2,7,18	210:2,6,24 211:11	one's
255:17 258:2,14	26:8 29:19 283:24	21:4 23:2,11,21	212:18 213:25	67:8
266:5 267:6,18	286:17	24:21 28:7,18,23	216:5,9,20 218:24	ones
268:15 271:8	odds	29:18,23 31:6,11	219:6,8 222:3,13	12:19 15:18 39:19
274:11 275:17	132:9 133:6,24,25	32:19 33:6,9,17	224:8,14,20 227:4	43:8,10 44:10
277:21 279:10	134:6,7,16,23	34:13 37:1,3,4,11	227:24 228:6	147:3 161:5 225:8
281:20 287:24	136:18,25 137:3	37:12,14 38:17,20	229:8 232:17	254:6 288:21
295:17 296:8,23	137:12,13 138:6	38:24 39:10 42:3	234:5,8,22 236:13	289:21,22,23
297:6 298:3 299:1	139:12,23 143:24	43:6,22,25 45:7	237:11 239:4	ongoing
299:11 300:1,21	155:11 161:15,23	49:9,14,24 53:4	240:25 242:15	283:7
301:24 304:11	162:4 227:13	53:16 55:18 60:23	243:13 244:1,7	online
305:20 306:5	234:23 235:11,14	61:8,16,23 62:19	245:19,22 246:1	154:1,6,12,22
307:2 308:9 309:3	235:16,17 240:20	64:14 68:3,10	250:6 251:14	159:5
309:12 313:24	241:10,13 242:12	73:19,21 76:17	261:12 264:21,25	onset
315:22 316:11	247:12 248:21	77:12 78:11 79:7	265:8 266:6	236:16
objections	253:6 255:12	79:23 80:14 84:22	269:10,20,23	operating
4:18 22:24 36:12	256:4 257:12,21	85:21 90:10 91:12	271:16 272:23	230:22 231:5
36:19	261:25 262:24	91:13,25 92:7,22	273:15,24 277:4	opine
objectively	263:7 264:22	93:24 95:13 96:20	278:7 279:25	102:23 254:19
232:1	267:12,14 268:1,2	100:25 101:12	280:6 282:11,19	296:20,25,25
observation	268:7,12,24 274:9	103:7 109:2	282:23 285:8	297:4
262:9	274:13	114:23,25 117:4,7	286:21 287:4	opined
observational	offer	117:19 120:5,21	288:13,22 294:2	66:6 102:13,19
6:16 166:17 176:11	37:18 76:4,8 86:20	122:10 124:14	294:13,17 297:8	116:8 119:11
228:22	192:19	125:2 126:11	297:23 299:12	opinion
observed	offered	129:3 132:13	300:23 302:11,13	31:22,23 43:17
104:12,15 110:16	125:15 189:14	133:1,19 135:20	303:4 307:18	47:1 56:9 65:2,8
142:7 171:12	offering	136:6,12 137:7,16	308:22 309:18,20	65:13 66:21 67:25
266:25 276:19	56:9 79:17,19 81:2	138:25 140:24	311:21 312:18,21	68:1 71:13 76:9
277:9	97:18 131:2 255:4	146:2,18 147:8,10	313:6 314:19	79:22 81:8 86:25
Obstetrics	offhand	147:11 148:25	315:1 317:3	87:3,6,13,14,24
147:21	114:22	151:1,9,20,24	old	88:13,13 109:10
obtaining	office	152:6,8,17 153:19	85:18 177:3	110:6,8 115:24
56:3	41:25	153:21,25 156:2,7	Omiencinski	116:4,10,11 117:7
obvious	officer	157:22 158:6	40:1	117:15,19,20
179:3	320:4	163:22 164:19	once	118:2 119:17
occupational	official	165:7,22 166:6	22:24 54:5 58:21	122:10,12 123:23
90:22 92:18 93:2	148:17	168:9,20 169:12	63:13 72:22 77:9	124:23 125:2,15
93:15 104:7,18,23	oh	174:6 175:25	97:15 112:25	126:5 148:17
105:2,8,9 106:5	20:16 78:12 114:3	176:4,9 179:18,21	130:19 163:18	153:5 169:11,12

178:5 181:19	organizations	138:22 139:3,18	304:2,5,10,19	165:9,10,10,12
197:6 206:11,14	146:10,10 147:17	140:16 142:14	305:5,13 307:25	211:14,15,15,17
214:3 224:5 255:4	149:16	143:1,15,25	310:12,16 311:2,9	219:23 259:14,15
294:23 295:4,10	original	144:18 145:9	311:13,15 312:2,5	259:15,17 278:3,6
295:16 296:6,9	283:20	146:4,12 147:1,19	312:23 313:9,12	280:11,14 302:17
297:23 298:2	originals	148:1,10 149:4,9	313:16 314:7,14	302:20 309:24,25
299:8,21 302:25	35:16	149:23 150:11,24	315:16,20 316:3,9	309:25 310:2
302:25 303:1,18	Ostbye	151:10 154:19	316:18,23	315:7,10 317:7,8
311:5,6,8,10,11	31:16	156:12,17,23,25	ovaries	page
312:1 313:8	outcome	157:2,4,13 158:13	298:19,24 299:10	4:2,11 21:4 33:13
opinions	197:19 320:17	160:20 161:11	299:15,23 300:7	38:21,24 39:1,4,5
30:14,17 31:8 32:2	outcomes	166:8,20 167:5,6	303:22	55:6,7 61:19
32:4,5,7,13 37:18	104:9	168:4 174:11	ovary	77:16,17 80:11
39:11 41:2 42:16	outlier	176:16 181:15	90:19 92:15	85:3 90:7,9,10
43:15 45:1 51:2	263:17 270:21	185:14 186:19	Over-speaking	91:25 92:4,9 94:5
67:3,4,9 75:21,22	outside	188:15 190:13	99:8	94:8 108:13
76:4,13 79:17,19	59:4,14 93:10	192:24 193:6	overall	111:20 128:2,2,4
81:2 86:9,20 88:1	121:22	196:25 197:7,8,20	26:11 52:8 116:4	132:8,15 135:11
97:18 115:20	ovarian	201:12 202:23	155:5,13 184:5,13	135:12,15 139:10
117:5,21,24 118:5	5:11,14,18,20 6:3,6	203:24 205:20	193:24 198:13	139:11 140:19
119:10,14,22	6:9,12,15,19,22	207:23 209:6	200:1 229:21	153:15,22 157:22
121:8 123:20	7:4,11,14,17,21	210:21 212:10	235:16 262:21	167:15,20,21
124:5,6 131:2	9:19,25 19:10	213:1 218:21,22	267:23,25	169:16,16 170:8
152:15 165:24	20:21 21:15 23:5	224:18 225:6	overestimate	174:1 176:9
175:23 179:15	25:12,16,21 26:9	226:4,17 227:16	160:12 226:13	180:14,16 184:24
180:12 197:21	26:25 27:5,10,15	228:11,17 229:25	overestimation	194:24 196:20
281:15,24 282:2	28:12 29:2 30:21	231:7 232:7,11	203:21 204:7	198:10 203:2,15
290:7,11 294:6	31:1,24 32:12	233:13,23 234:24	overlap	207:11,18 210:7,8
298:4 310:11	40:19 48:15 52:3	237:16 245:11,15	16:5,6 161:5	210:9 211:19
312:22 313:20	52:9 54:15 56:21	245:21 246:9,24	overlapping	212:19 215:25
opportunity	58:17 60:4 62:21	247:7 249:13	161:1	219:25 220:1,25
17:10 78:7 164:1	63:21,24,25 66:2	251:10 252:25	oversight	221:8 222:4,4
311:21 312:9	87:1,5,12,14	253:11,25 254:4,8	23:6,9	224:9,9,14 226:7
opposed	88:23 89:1,11,17	254:16 255:8	overstating	232:23 233:4,5
316:23	93:4,9 94:12,14	257:25 259:22	303:8	234:2 235:2 238:6
opposite	94:19 98:5,14	263:25 265:5,20	ovulation	240:5,23 244:1,7
232:2 277:20	102:8,12,15,23	266:3,20 267:22	40:19	251:14,20 253:20
oral	103:20 105:11,15	267:24 270:8		255:1 259:19,20
4:15,19 36:19	108:8,22 109:14	271:25 278:13	P	260:8,20 262:5,5
127:3 254:1,3	109:22 110:10	285:10,14,17	P	264:18 270:2
305:9	111:9,10,13 113:1	286:14,20 291:21	2:1,1 3:1,1 8:1	271:16 272:11
ORANGE	117:14 120:19	292:5,13,14	p-value	274:25 278:7
320:2	122:13,17 124:3	294:25 295:2,4,7	274:19	282:13 298:12
order	124:24 125:6,8	295:20,22 296:7	p-values	307:21 319:5
245:8 308:23	127:4 128:11,20	297:5,10,13	274:22	pages
organization	135:13,18 136:7	298:16 299:25	p.m	320:10
148:18 251:10	137:1 138:17,20	303:2,5,9,14,19	115:4,6 116:21,24	paginated

151:16	22:19 28:7,8 29:6	59:10 60:14 61:1	172:22 173:2	15:11,15 16:19
paid	30:5 112:21,23	61:11 62:8,23	174:19,25 175:9	23:9 48:1 60:12
73:6,10 124:15	122:16 138:19	63:6,12 64:5 65:6	176:6 177:1,14	67:22 68:1 88:15
127:20 174:17,21	165:16 188:24	65:15,19 66:17	178:9 179:9,23	100:6 105:13,17
174:23 179:7,11	191:13 194:11	67:6 68:6,22	180:2 181:3	108:7 116:2
paper	228:24 246:16,21	69:20,24 71:15	182:13 184:4,18	126:11 127:4,7
7:19 19:17,18	247:14 250:8	72:17,24 73:8,14	186:1 188:16	166:16 202:8,9
20:23 21:5,8,12	273:20 277:18	73:24 74:10,25	189:17,25 190:6	214:11 229:20
23:17 25:5,6,14	287:21 292:15	76:7 77:7,10 78:4	190:15 192:16,25	254:2 262:20
25:17,22 26:7,13	307:6	78:8,12,20 80:23	193:14 194:5,14	271:1 277:23
26:16,22,25 27:3	paperwork	81:6,20 82:5,19	195:24 196:12,17	309:10
27:9,13,21,22	28:1	83:12,22 84:9,17	197:23 199:2,16	partial
28:2,3,11,20,22	paragraph	84:19,25 86:2	200:20 201:3,15	78:20
28:23 29:11,12,14	78:5 90:12 92:8	87:16 88:4 89:2	201:17,22,25	participants
29:17 107:22	93:14 94:8 95:24	89:12,21 91:7,18	204:15,22 206:2	130:7 189:23
108:4,6 109:3,13	108:15 109:24	91:23 93:16,21	206:12 207:1	191:18 203:23
135:12,22 136:5,7	128:4,6,7,8	94:22 95:3 96:5	208:3 209:12,21	217:24 218:1
136:22 138:3,21	130:14 131:22,25	96:13 97:14,21	213:22 214:4	219:12 234:24,25
138:24,25 139:12	132:14 135:15,17	98:9,19 99:1,7,11	219:18 228:15	236:17 284:3,22
140:9,17 157:3	140:20 150:8	99:18 100:3,9,20	229:18 230:4	participating
165:15 173:6,7,9	158:1 167:16,17	101:3,9,21 102:16	234:7 236:11	284:24
174:13,15 176:5	167:23,24 180:15	104:1,24 105:24	241:15 242:9,14	particular
178:24 179:1,19	180:16 196:21	107:7 108:9 109:5	245:23 246:20	12:2 41:22 56:9
179:21 180:6,12	210:14 211:23	109:16 110:7,25	247:3,24 248:2,11	75:11 138:5 200:9
181:9 182:24	212:20,21 216:2	112:13 113:5,19	250:23 251:4	221:19 232:20
183:2 185:4 187:3	221:11 233:8	113:25 114:20	255:17 258:2,14	242:17 243:16
189:4,9 190:13,14	238:7 240:9 241:1	115:1,15 116:1,13	259:2,11 266:5	288:1 297:4,8
192:11,23 193:6	260:9,24 262:6,7	116:19 118:1,16	267:6,18 268:15	299:9 301:21
193:12 195:7,11	270:4 275:1	119:1,19 120:9,20	271:8,10 273:12	particularly
202:19 204:13,25	298:13	122:6,14 123:10	274:11 275:17	45:2 47:5 136:15
205:4,7,25 206:10	Parfitt	123:25 124:10,12	276:24 277:21	158:10 220:19
208:24 214:9,17	2:5 4:6 8:24,24	124:25 125:17	279:10 280:5,7	222:9 223:9,24
216:15 217:3,5	12:11,21 15:23	126:3 127:17,23	281:20 287:24	238:11
226:22 228:10	16:1,4 20:12,17	129:6 130:18	295:17 296:8,23	parties
229:17,22 230:15	22:20 23:1 25:1	131:14 132:4	297:6 298:3 299:1	121:20 320:13,16
232:12 234:3,13	26:23 27:7 29:13	133:5,11 134:18	299:11 300:1,21	partly
234:22 236:15	32:25 34:6,11	135:6 137:9	301:24 304:11	210:17
242:2 243:3 269:4	35:12 36:4,11,14	142:16 143:16	305:20 306:5	parts
269:12 274:16	36:16 37:21 38:1	144:20 145:11	307:2 308:2,9,13	38:17 144:13
276:9,10,13	41:5,23 42:8,18	148:15 149:11,18	308:17 309:3,12	pass
277:17,23 279:6	45:23 46:8,14	152:11 153:6	309:21 310:4	84:23 136:10
286:14,18 288:1,6	47:19 48:3,22	157:17 160:7	314:4,22 315:5,22	294:11
306:18,20 307:5	49:5,15,20,22	161:2,18 162:14	316:11 317:4	passive
307:10,22	50:12,19 51:24	162:21 163:17	Park	259:24 260:7
paper's	52:14 54:10 55:1	167:10 168:11	2:22 20:19 25:6,9	pathologist
306:24	55:3,5,8,12,20	170:4 171:7,17,20	26:2,22	54:5,7,14,18
papers	57:14 58:3,12	171:24 172:3,8,18	part	pathologists

54:7 316:14	76:3 104:10 105:1	191:8,14,16,17,23	phrased	260:15 297:19
pathology	105:14 112:5	192:10 193:10	297:17	309:6,15 313:14
54:4,6,9,13,14,21	142:4,6 144:12	194:10 208:9	phraseology	plausible
55:15 56:4	193:18,23 199:20	217:12 220:11	234:16	182:6 183:10
patients	199:25 200:5,7	282:16 301:1	phrasing	231:24
32:12	220:10 221:5	305:23 306:4,9	103:3 149:2 241:7	play
Patricia	228:23 255:23,24	peritoneal	physician	231:13,23
1:12 4:10,12,13,15	262:1 274:20	5:17 6:4 99:12,23	288:18	please
4:19,21,23,24 5:4	301:1	100:4 138:22	PI	8:6 9:16 14:13
5:15 8:5 9:2,17	people's	139:24 151:11	284:20	19:21 24:22 61:9
36:20 41:16 317:6	44:19	permitting	picture	61:20 64:22 70:3
318:2 319:3	percent	291:19	214:12	70:4 77:4 78:22
patterns	59:15 60:11 134:13	person	piece	101:9 111:18
182:4	134:20 137:17	11:8	66:23	115:18,18 172:12
Paul	155:3,4,6,8,11	person's	pieces	173:19 186:3
7:18	166:7 236:5,7,13	223:17	312:12,15	200:14 219:19
pause	236:13 247:22	personal	pile	228:4 237:12
187:11	248:5 249:13	3:11 8:18 206:11	37:1 183:15	282:9 299:5
PCPC	250:1 256:12	222:20 223:8,21	pinpoint	309:22
310:8	262:23 303:9	223:22 281:17,22	102:24 295:5,19	pleasure
PDQ	313:11	294:15,20	305:10	9:11
6:3,4 151:3,10,21	percentage	personally	place	plenty
153:13 155:23	185:3 303:14	45:16 233:25	33:11 162:18 235:3	145:14
292:21 293:9,17	Peres	290:20	Plaintiff	PLLC
peer	23:17	perspective	11:16 72:18 310:3	2:12
26:19 30:14 286:1	perfect	86:13	Plaintiffs	PLOS
peer-reviewed	275:24 276:2	perspectives	2:2 8:23,25 9:22	7:6
65:2,8,14,25 68:2	perfectly	44:20	16:25 21:10 30:7	plot
69:3 72:9 74:23	275:13	pertain	31:23 36:13,18	194:25
75:2 81:9,18,24	performed	26:1,5 30:10 80:4	73:7,10 86:21	plots
82:12	121:19 163:1,4	226:17	106:7 124:15	268:6
Penninkilampi	212:4 269:6	pertained	174:24 271:4	Plunkett
6:8 147:24 164:22	313:19	314:13	Plaintiffs'	291:4,8
165:15 166:4	perineal	pertaining	4:18 8:21 14:16	Plunkett's
167:14,18 168:21	6:6,11,14,21 7:16	13:8 19:10,14 22:5	17:3 40:14 41:24	291:10
183:13,17 184:3	7:20 96:11,20	59:9 64:3,7 75:5	43:22,25 44:12	point
185:19 186:12	97:13 98:17 99:22	75:17 85:8 87:13	48:21 49:4 59:22	28:5,16 51:13,18
187:20 191:15,19	100:7,16,16,22	109:18 253:21	67:20 68:5,8	79:21 102:18,22
192:9 193:11,20	101:17 151:25	279:12	72:10,15,21 73:3	138:8 142:1
194:2 206:23,23	166:6 168:1	ph	82:16 83:17	144:11 147:14
207:25 208:21	174:10 176:14	1:24	145:25 289:9,17	159:24 178:13,14
216:22,25 217:3	185:13 202:22	Ph.D	290:11 291:16	178:17 179:5
217:24	205:19 265:19	1:12 4:10,12,14,21	planning	190:16 204:6
Penninkilampi's	266:4	4:24 5:5 9:2	284:6	226:22 228:21
217:9	period	318:2 319:3	plausibility	229:3,6,21 237:9
people	16:13 113:22 114:7	Pharmacopeial	117:12 121:5	239:10 247:15,20
12:24 15:24 45:2	160:21 189:20,22	83:10	156:24 205:16	256:11 257:6

258:18 259:3	48:14 96:17,24	82:14 83:2,9 84:4	66:7 200:3 211:20	preretirement
269:12 289:1	97:10,23,25 98:21	86:1,10,22,24	212:2,9,12 213:4	10:16 282:17
293:7,14 295:3,15	101:23,24 102:1	87:4,7,8,11 88:2,7	213:9,21 214:3,9	presence
295:19	104:7 107:3	88:11,15,17,22	214:11,16,18	76:14 83:5 96:2
pointed	110:15 147:13,14	94:7,20 102:12,14	215:3,11,13,16,17	117:22,24 118:5
266:22	190:10 239:14	105:11,22 106:8	284:19	119:15 121:8,14
pointing	255:11 257:5	106:13 109:20	practice	123:4,8
230:15	286:10 291:18,25	111:12 112:8	224:22	present
points	303:21 307:1,25	113:21,24 114:7,9	practices	118:25 270:8 275:4
51:14 238:4 274:22	308:7	114:13,14,17	1:6 281:25 282:1	presentations
policies	possibly	116:3,4 117:9,13	pragmatic	30:20
22:9	66:23 146:14 253:3	117:16,22,25	300:4	presented
Pollak	257:8 296:16	118:6,8,19 119:16	pre-	73:22 74:18 111:3
31:16	post-2014	119:22 120:4	240:16	121:10 148:17
pooled	235:23 236:5	121:1,6,9,14,16	pre-2014	presents
6:19 179:14,18	post-data	121:24 122:3	235:22 236:4	110:23
population	240:16	123:24 124:20,23	precede	preserve
132:21 138:3,15	post-interview	125:4,7,13,19	177:9	24:21
261:7,13,23 262:1	225:11	126:5,22 128:22	preceded	presume
304:18	postings	128:24 129:4,9,10	314:19	20:11
populations	30:16,17	129:10,24 130:3	preceding	pretty
304:24	potential	130:17,23,24	203:15	63:22,23 71:12
portion	19:19 20:24 21:6	131:17 132:2	precise	72:6 111:13 162:7
57:23 86:18 95:14	23:8 26:22 28:13	150:11 202:22	57:11 129:8,11	182:8 229:21
171:23 213:15	86:16 87:10 94:11	203:25 223:17	130:20 146:7	231:1 240:9
219:1 241:10,13	107:2,16 109:25	237:15 239:15	172:20 214:16	242:23 278:23
307:20	110:13 117:13	265:19 266:11	265:1 307:19	316:6
position	122:19 164:12	267:10 276:18	precisely	prevalence
70:22 71:1,3,8,10	182:25 203:7,12	277:8 278:11,21	91:6 118:17	130:12,17 260:21
263:24	203:13,18,21	279:14 281:9,12	precision	261:2,6,12 304:23
positions	204:7,7,8 218:20	281:16 285:18	221:3	Prevention
149:15	230:12 231:17,20	291:21 292:4,6,7	pregnancy	6:4
positive	240:15 241:19	294:24 296:1,3	224:2 305:9	previously
90:21 92:16 93:3	270:15	298:1 303:19,24	premature	48:17 50:15,22
94:2 138:11 162:1	potentially	304:1,5,9,23	108:23	82:21 181:16
176:18 211:4	190:20 261:23	310:12 311:6,9	preparation	185:2 296:13
287:15,22 288:7	306:10	312:2,4,22 313:9	19:2 26:8 37:5 38:8	297:12 301:16
possession	powder	314:6,14 319:2	38:9 313:20	primarily
24:17 36:1	1:6 6:18,22 7:11,14	powders	prepare	112:5,25 125:3
possibilities	52:2 64:4,8,19	9:25 93:11 96:3,3	45:15,16 46:20	primary
218:11	65:4,18 66:13	96:10 120:18	prepared	5:17 6:4 52:1 63:14
possibility	68:20,25 69:7,9	123:5,5,9 129:13	15:7 16:8 32:15	135:23 138:22
185:23 205:13	70:13,15,18,19	129:16,19,20	46:22,24 291:2	139:24 151:11
223:16 238:23	71:1 75:6,18,24	131:8,8,9,11	292:19	print
239:11 240:1,19	76:2,5,10,14	140:10 180:19	preparing	153:12
241:23 257:13	79:20,23,25 80:1	278:18	12:6,17 17:13	Printout
possible	80:10 81:10,14,22	power	34:17,17 150:21	5:20

prior 14:22 15:18 22:19 33:9 38:7 56:8 88:7 141:17 161:6 162:11 176:19 180:4 218:1 219:12 233:14,23 234:1 236:24 300:18	product 76:2 117:13 119:25 129:10,24 130:4 296:10 298:1 products 1:6,7 3:11 8:18 64:4,19 65:4,18 66:8,14 68:21 69:1,9 70:16,19 71:1,18,20,22 75:6,8,13,14,18 75:20,24 76:6,10 76:14 77:25 79:5 79:12,20,23,25 80:1,2,4,5,7,16 81:11,13,14,22 82:14 83:2,9 84:4 85:15 86:1,11,22 86:24 87:4,7,9,11 88:8,11,15 102:12 102:15 105:11,19 105:23 106:6,8,14 109:20 111:12 112:8 113:22 114:7,10,13,14,17 116:3,5 117:9,16 117:22,25 118:6,8 118:19,25 119:16 119:22 120:4 121:1,6,9,14,15 121:17,21,25 122:3,4 123:24,24 124:20,23 125:5,7 125:13,20 126:5 126:23 281:9,12 281:16 294:15,21 294:24 296:1,4,11 297:19,20 298:8 298:10 303:19,24 310:12 311:6,9 312:2,4,22 313:9 314:6,14	professionals 32:11 professor 10:10 profiles 315:21 progress 27:17 28:9,11 30:10 progressed 160:20 promised 232:16 prone 185:7 207:13 pronounce 196:2 pronounced 123:18 316:1 proper 133:22 proportion 80:1 Proposal 174:2 proposition 124:22 203:10 204:5 226:10 272:23 273:8,21 prospective 7:4 203:5 207:21 210:17 211:1,3 227:14,20 228:2 228:13 229:12 230:2 prospectively 202:24 205:18 206:4 prove 79:10 proven 255:16 provide 34:15 40:14 67:8 69:4 72:22 74:2 83:17,20 91:11 116:9 141:8	145:25 199:21 214:19 226:11 305:3 provided 17:9 18:17 35:23 39:13 40:2,11,24 42:12 44:14 46:25 47:1 48:21 49:4,7 67:20,23,24 68:7 68:16 69:2 72:10 72:14,19 74:1,7 77:3 80:15 82:16 85:13 115:20 118:23 141:21 144:9 149:8 289:16 293:15 294:5 296:21 306:17 provides 87:10 194:10 231:18 providing 65:13 67:3,4 81:18 141:17 142:20 PTI 3:17 8:19 public 30:24,25 47:16 48:1 166:12,24 261:8,17,18,23 320:3 publication 22:4 188:10,20 189:3,7,12,14 196:14 237:8 242:7 244:14,17 253:4,9 283:23 285:20 315:15 publications 19:9 26:5 32:16 41:9 47:11 243:2 285:25 286:8 publicity 233:22 240:12 publish 65:2,7 published	21:19,24 23:24 48:5 67:4 81:18 95:18 98:2 110:11 127:3 135:22 138:16,19 147:3 148:11 158:18,22 160:25 161:4,6 162:1,16 177:24 186:24 188:13,18 188:24 193:13 241:17,18 243:9 243:20,22 244:19 244:23 254:19 255:4,9 306:12 315:14 publishing 138:21 302:7 pull 146:6 161:11 234:5 purchasing 130:4 pure 296:6 purported 76:5 89:10 126:13 150:23 purpose 27:8,12 128:18 162:15 202:21 284:14 purposes 20:2 27:3 34:17,22 95:16 312:21 313:19 put 78:24 103:17 159:1 255:8 284:15 287:18 314:9 putting 75:24 pyramid 159:1 301:18 302:1 <hr/> Q <hr/> qualification 178:23 qualified
--	---	---	---	--

55:22	267:8 271:13	262:14	253:6 255:12	185:2,5 195:12
qualitatively	283:16 286:7,21	raise	256:4,6,25 257:12	196:21 198:11
106:6 142:24	286:25 294:3	164:2 225:24	257:14,21 258:7	199:18 202:20
quality	307:20 308:2,5,21	raised	268:2,2,7,12	203:4,17 204:2
25:20 127:6	310:10,15	205:15 306:11	raw	205:9,22 207:17
quantify	questioned	ran	77:24	207:19 210:14
72:3	311:17 314:5	206:20	RDR	212:22 221:11
quantitatively	questionnaire	randomized	1:21 320:22	222:6 233:8 237:9
142:25	129:2 131:16	166:22	re-ask	238:8 239:13
quantity	140:11 191:20	range	79:18	241:4,7 247:14
49:7 76:9	286:25	134:17,20 137:13	reach	251:20 259:21
quarrel	questions	237:1 248:22	111:9 125:14	261:4 262:8
85:24 86:6	13:25 14:12 16:16	255:15,20 256:11	126:25 155:18	265:18 269:13
quartiles	31:5 36:6 37:2	256:17,19 257:23	182:18 231:2	270:5 271:22
276:22 277:12	55:3 62:11 78:7	ranked	256:25 263:3	272:12,21 275:3
question	113:6 164:1	302:2	308:24 309:11	275:20,21 276:17
15:18 28:18 29:15	171:19 184:10	rappel@seyfarth...	reached	276:23 277:7,14
50:15,22 54:22	201:10 205:16	3:15	95:12 97:20 156:9	277:16 278:8,15
55:14,16 56:13	209:25 220:13	rare	178:14 227:13,21	285:21 289:20
57:11 58:15 60:5	223:12,22 224:25	114:11 310:25	252:7 268:19	291:10,11,18
61:21 63:14 64:15	225:16 280:1,4	rate	299:15 300:7	298:5,14,20 318:3
64:20 65:21 66:18	294:22 302:12	14:18 236:5,7,18	reaches	319:5
68:24 70:2,3,4	310:7 314:23	rates	298:18,23 299:10	reader
74:5 77:9 87:18	315:1	111:23 112:10	299:23	22:7 160:15 168:21
98:25 99:2,6,19	quick	113:24 114:8	reaching	170:1 175:7
101:16 102:4	117:2 306:16	236:6,10	141:4 161:15	176:23
109:3 110:24	quickly	ratio	reaction	readers
117:3 119:9 120:3	148:4	132:9 133:7,24,25	231:19	171:4
120:22 124:3	quite	134:6,7,16,23	read	reading
125:19 126:1	29:24 64:9 101:4	136:18 137:3,12	39:13,17 43:12	56:13 77:19 91:3
129:1 131:16	138:19 140:2	137:13 138:6	59:12,19,25 60:7	94:16 117:10
135:8 144:6	174:13 209:8	139:23 143:24	64:9,10,23,24	120:21 144:14
146:21 156:14	218:13 237:13	155:11 161:16,24	71:6,6 72:7,8	145:21 150:13
163:9,24 172:4,7	262:9 263:8,17	162:4 235:11,14	76:23 77:21 78:2	158:4 170:14
172:19 175:4	276:25 295:7,22	235:16,17 241:10	79:1,9 85:12,23	185:17 197:4
177:20 178:11,11	295:22 314:17	241:13 242:12	90:16 92:11,23	213:13 226:14,16
178:20 183:5	quote	248:22 257:24	94:9 99:4 108:18	228:4 238:15
184:16 187:19	103:4 150:9 167:18	261:25 262:24	108:25 111:1	240:3 251:25
189:2 200:14,15	203:16	263:7 264:22	118:3 128:9	254:22 260:1
200:21,22 202:1	quoted	266:12 267:12,14	132:17,24 140:25	291:15 298:13
206:19,21 219:3,4	80:20	268:24 274:9,13	141:10 145:22	300:3
219:5,8,9,10		rationale	150:9 154:16	reads
223:14 227:17	R	188:1	158:8,16 162:25	278:8 319:5
232:8,16 245:17	R	ratios	167:25 169:19	ready
249:4,5,6 252:19	2:1 3:1 8:1 319:1,1	136:25 139:12	170:10,19,20	28:6 52:21 259:9
254:22 255:6	320:1	227:13 234:23	173:20 174:6	real
258:17 265:2	race	240:20 247:12	176:10 180:17	193:25 247:16

249:2,5,6 257:13 257:17 316:17 really 44:25 51:16 86:15 142:8 155:17 163:23 171:9 187:13 188:6 197:11 211:2 214:20 225:2 230:2,15 231:3 258:15,16 259:20 263:17 265:1 298:7 303:15 310:20 realtime 99:5 148:22 reason 85:24 116:15 178:22 203:18 204:7 214:1,6,8 214:10 222:3 224:1 230:13 239:8 reasonable 284:21 reasons 161:10 180:3 215:23 232:25 241:25 242:21 251:7 263:2 300:4 REATH 2:21 Rebecca 44:6 rebut 68:19 73:23 74:19 rebutting 118:24 recall 7:14 10:3,6 11:17 13:17 17:6,13 22:1 24:6 40:1,3,9 44:11 54:20,22 66:9 69:15 75:9 75:14 76:16 83:19 96:6 103:17 104:18 107:13	110:11 112:2 115:10 118:19 123:11 132:23 135:25 138:21 146:5 149:5,7,12 150:5 159:18,18 160:4 164:11 185:7,20 186:6,11 192:21 203:7,12 203:14,22 204:9 204:10 205:14 207:13 218:9,12 218:13 220:11,18 220:23,24,24 221:1,1,2,5,7,12 221:18 226:11,22 229:2,3,14 230:7 230:7,12 231:4,4 231:11,12,17,20 232:5,9,13,20 234:19 237:16 238:10,24 239:7 239:12,22 240:1 240:11,13,16,19 241:6,14,19,24 242:4,5,8,20,21 243:4,10,17 251:3 251:12 252:13,13 252:20 253:16 254:10 283:9 287:8 292:23 295:14 300:13 311:19 314:7,16 recalling 149:1 242:16 307:5 Received 92:24 Recess 52:17 115:4 165:10 211:15 259:15 309:25 recognize 18:3 56:16,17 57:6 79:25 103:24 106:21 160:9 316:13 recognized	290:1 recognizing 57:3 161:9 284:17 recollection 146:2 recommendations 311:22 record 8:3,7 9:16 20:2 21:2 36:15 41:23 50:4 52:15,18 73:25 74:14 91:19 95:16 100:5,12 115:2,5 116:20,22 116:23 165:8,11 199:17,17 211:13 211:16 219:16,20 219:21,22 259:13 259:16 278:1,2,4 278:5 280:10,12 280:13 302:15,16 302:18,19 309:21 309:23 310:1 315:6,8,9 317:7 reduced 154:8 155:9 reducing 10:17 reduction 155:3 REES 3:3 refer 17:16 54:25 61:8 115:21 120:10 123:15 128:3 133:20,22 134:8 134:12 135:12,18 137:23,25 138:4 138:10 163:10,11 164:10 166:19 183:6,9 194:8 207:6 246:3,18 250:9 288:17 295:25 reference 39:8,10,18 40:18	41:3 45:19 46:6 76:20,23 216:24 246:17 278:25 referenced 39:15 75:5 139:6 references 5:3 33:20 38:22 39:10 45:25 46:4 46:17,22 47:7,10 47:13,15 49:10,17 49:18 50:17,25,25 51:1,5,7,9,9,15,16 51:19,20 115:9 referred 40:21 60:1 111:16 124:8 183:24 208:22 246:25 247:8 270:21 referring 11:10 20:19 62:3 67:19 79:22 80:11 91:15 96:13 107:9 107:11 115:10 120:11 147:6 148:7,13 151:3 179:6 215:14 216:16,21 246:22 260:3,11,14 266:8 274:23 296:1 300:18 refers 182:24 238:3 246:9 246:12 reflect 18:6 73:25 100:5 238:24 273:8 274:8 reflected 216:15 217:5 292:2 reflecting 299:16 reflection 136:16 reflective 262:18 267:16 273:1 reflects	110:8 236:1,3 269:23 274:16 279:23 regard 12:15,19 59:6 75:4 82:15 116:11 117:6 120:2 121:8 122:8,23 124:3,5 124:18 142:12,14 147:12 154:14 156:10 168:3 213:21 222:7 243:10 253:19 272:6 286:17 292:13 297:15 302:24 303:17 305:16 310:10 313:3,8 314:6 315:19 regarded 142:10 regarding 73:3 282:4 283:24 regards 56:3 120:23 region 223:18 regulatory 25:23 Reid 5:13 107:22,25 108:3,6 reject 250:12 relate 310:11 related 5:6 15:15 16:12 21:15 48:14 58:17 59:16 60:19 64:24 66:1 68:15 142:3 181:14 260:6 284:15 285:14 320:13 RELATES 1:9 relation
---	---	---	---	--

122:17 230:19 253:17 254:4 286:14 304:5 relationship 63:20 139:23 176:13 194:12 205:19 253:12 relationships 158:12 relative 158:13 160:12 205:10 213:6 221:14 251:22 255:20 264:5 270:22 320:14 relatively 26:10 27:10 104:8 136:16 275:12 310:25 relevant 60:3,9 127:8,10 219:15 233:9 273:25 298:17 reliance 4:24 45:5,17,18 relied 119:5 126:24 298:25 299:7 religious 25:15 rely 41:1 54:6 117:23 210:10 300:4 301:5 308:24 309:7 relying 41:6 120:7 166:16 241:12,12 remark 256:6 remarkable 45:1 remember 21:25 112:21 191:10,12 212:11 221:3 287:12 293:6 307:6	310:13,17 remind 84:15 reminder 13:25 294:19 rendered 123:5 298:1 rendering 312:21 renders 96:3 123:24 Renée 3:15 8:17 294:20 repeated 134:22 repeatedly 255:7 268:21 271:13 rephrase 14:11,13 101:6 106:2 180:25 215:1 282:12 286:5 299:4 replicated 262:11 report 4:21 5:3 6:11 12:17 13:8,16 26:6 30:14 32:17 33:21 34:17 36:3 37:7 37:15,17,22 38:7 38:9,13,15,17 39:12,15,20 42:13 42:16,21,22 43:16 44:4,24 45:20 46:5,12,13,21 47:25 48:10 49:3 49:11 50:6 51:1,3 51:6,10,14 57:8 66:5,10,20 69:8 69:13,14 71:21 75:17 76:18 78:18 79:23 80:9,21 88:3 90:7 93:25 95:2,11 97:16,19 98:1,3 108:4 112:24 115:8,11	116:8 118:13 119:11,14 120:7,8 120:11,11,24 122:25 123:15,15 123:19 128:3 129:3 130:10 132:1,6 133:1,9 134:4,19 135:5,11 136:3,22 139:1,12 140:14,19 144:10 144:14 150:21 152:18,22 157:23 159:23 160:16,17 162:18 164:6,6,9 164:12,18 168:20 168:24 170:2,5 171:5,9 172:14,20 173:1 175:3,6,7 175:11 176:23,24 177:4,5 183:18,22 186:6 187:4 191:2 191:22 193:10 195:3,6 196:20 198:10 204:8 206:18,25 207:7 211:19 213:21 215:5,9 216:10 218:6 219:25 220:22 221:8 222:4,12 223:7 226:19 227:25 235:21 240:14,18 242:13 243:14 244:2 245:12 251:15 252:22,24 253:14 254:20 255:5,9,14 256:2 257:10,23 258:6 259:19 264:21 265:11 267:2 268:24 271:19 274:13 275:24 277:24 279:3 289:13 292:1,19 293:19,22,23 294:4,8,24 298:12 301:4 302:7,8	303:18 307:24 309:6 313:20 reported 1:21 23:20 88:6 112:22 130:23 134:6 136:12,21 136:22,24 139:16 139:23 140:1,14 142:6 160:1,11 163:6 185:3 187:1 187:5,23 189:4,9 216:18 220:5,7,17 228:25 231:14 235:15,23 236:4,6 236:6,10 239:17 255:20 271:20,24 279:8,21,22 292:15,16 296:4 reporter 8:7 14:3 100:4,11 116:17 320:3 reporting 203:25 217:9,10 236:17 reports 42:20 43:18,23 44:1,13,16,22 67:3 73:2,19,25 74:7,15,22 112:18 118:15 127:21 187:23 216:25 238:7 255:19 289:9,20 290:14 290:15 291:3,16 represent 147:17 280:20 294:20 representation 55:24 represents 50:5 148:13 reputation 290:6 request 24:25 84:3 283:17 requests 33:15	required 21:16 requirements 21:23 22:1 reread 19:4 286:4 research 6:11,13,18 7:6,10 127:6 174:2 224:23 243:24 283:20 285:9 researchers 254:2 reservations 168:22 170:3 172:21,24 reserve 172:1,4 reserved 175:8 176:24 317:9 reserving 181:1 respect 27:21 29:10 56:20 67:11,19 68:3 70:22 75:16 93:9 94:6 121:20 126:1 136:1 137:3 142:24 149:9 156:25 163:8 188:12,25 190:13 214:16 216:1,9 220:13 224:18 252:7 281:18 285:24 308:11,20 respectfully 163:23 218:25 respond 23:19 33:25 responded 24:8 62:12 response 4:18 36:18 226:2 responsive 34:4 200:13 rest 291:15
---	--	--	---	--

restate 87:18 117:3 225:12 258:4	38:9 43:14,18,20 44:16 47:3,5 51:22,23 56:11,22	56:7 67:25 78:23 93:12 101:15,20 102:4 109:21	149:3,3 154:19 155:3,4,10 156:12 160:13 163:11	Ross 6:8
restricted 278:17	56:25 57:12,19 58:1,10,19,25	114:22 123:16 131:21,22 135:20	166:7,15 167:2,5 174:11 176:15	Rothman's 288:15
result 213:7 221:13 264:7	60:2,12,24 61:22 62:2,17,20 63:3	135:20,23 136:2 137:18 139:15,16	181:15,16,20,24 181:25 182:5,7,24	roughly 155:1,6 161:23 202:6 218:16 303:9
results 77:18 79:2 80:3 132:3 135:25 140:13 142:7 169:20 170:10,16 170:21,23 171:10 172:15 185:6 195:13,20,22 196:8 213:12 215:19 227:18,20 227:22 228:5 229:11,11,17 230:25 231:2,5,8 231:11 232:5 238:18,24 264:18 268:18 269:14 279:8	63:10,15,19 64:2 64:6,17 65:5,9,11 66:14,22 67:12 82:3 89:9 112:1 113:3 127:11 156:15,18 157:6 167:8 253:20 254:3,7 280:3 286:1 291:6 293:12,13 311:22 311:24 312:9,13 313:18 314:6	140:10 141:14,19 144:24 148:8,23 153:1 162:13 171:3 172:19 178:4 179:2 191:9 191:25 195:23 196:8 199:4 202:18 203:17 205:8 207:14 210:4 212:20 216:11 221:20 222:1,11 227:15 227:22 228:8,14 231:9 233:4 235:6 235:24 236:18 240:23 252:8,21 256:20 257:16 261:10 266:1 268:1 269:7 270:3 274:19,24 275:9 282:17 286:13 289:4 293:7 306:2 310:15,19 311:4 311:12,24	182:25,25 183:7,9 183:11 185:3 186:8 187:6 196:25 202:23 203:20 205:20 210:20 213:6 221:14 224:25 225:1,8,9 226:23 230:9 232:14 237:16 247:10,21 247:22 248:6 249:13 250:1 255:20,22 256:12 261:24 263:4,5 264:5 265:5,21 266:3 270:7,22 272:19 276:20 277:10 278:10 285:10 286:19,22 292:16 295:7,20 295:21 296:7 297:5,9 303:23 305:6,9,15 306:7 306:11,13 313:12 315:21 316:5,6,22	route 303:21 routes 105:16 regularly 314:1,2 RPR 1:21 rule 4:21 110:14 241:23 ruled 103:15 242:8 rules 13:23 runner 38:3 running 264:25 307:19
retained 11:20 88:3 292:5 295:11	reviewed 34:16,22 39:23 40:6 42:24 43:2,2 43:4,5,8,11,11,20 44:1,2 60:19 61:6 67:15,17,22 72:9 72:13 73:19 74:23 75:5,16,19 76:13 82:16 85:21 103:21 118:15 157:8 159:23 165:23 175:13,23 214:24 289:6,8,12 307:9 312:24 313:7	right-hand 92:7 94:7 180:17 238:2 240:6	risks 158:14 251:22 254:10	<hr/> S <hr/>
retire 282:24 283:1	reviewers 166:19	risk 5:14 6:9,12,14,18 6:22 7:14,17,21 19:10 20:21 23:4 25:12 26:14,25 27:10,14,16 28:12 30:22 31:1 105:15 114:15,17 117:14 122:17 124:18 125:6,23 127:4 131:20 134:14 135:13,24 136:8 147:25 148:21	RMR 1:21 Road 2:3,12 role 7:14 237:16 314:14 rolling 116:15 room 182:21 Rosenberg 29:25	S 2:1 3:1 8:1 S-I-N-G-H 291:8 Saed 48:13 safe 76:1 86:14 168:2 sales 1:6 130:22 sample 104:19 136:17 140:2 187:17 237:3 samples 77:24 79:4 80:15 134:23 saw 68:10 72:22 230:13
retirement 282:19	reviewing 40:2,3 44:22 45:2 71:25 76:16 82:18 82:23 290:14			
retrograde 94:11	reviews 127:3 272:2 314:3			
retrospective 228:2,14 230:1	revisit 306:11			
returned 232:22	right 20:5 33:11 39:5 41:14 50:2 55:9			
returning 103:19 123:14 177:18 183:13 187:19				
reveal 222:25				
review 5:9,12 6:7,9 7:19 17:10 19:1 21:23 26:19 30:14 38:7				

247:12	57:5 68:17 69:17	25:13 33:14 37:22	288:15 293:1	214:22,23 240:4,8
saying	70:7	38:21,25 44:20	299:2 305:13	241:3 244:11
14:4,5 69:3,6,7	scientists	45:12 47:21 49:24	307:23	259:20 260:5
81:24 97:24,25	85:25 86:4,4 141:1	50:1,7 55:14,16	seeing	262:7 276:17
98:5,7,11 100:6	142:1,8 145:1	61:24 65:24 74:9	95:7 154:3 241:11	277:5 300:2
103:4 134:15,15	157:11	74:11 77:15,17,19	seen	307:23,24
166:21 178:18	scope	80:10 84:10 85:6	33:6 41:19,21 74:8	sentences
195:19 196:7,9	37:18	85:9,10,19,20	77:13 84:2 85:4	203:16
215:17 220:13	Scott	90:11,13 91:3	107:25 150:3	separate
229:10 232:3,15	2:19 8:9 9:10 37:21	92:5,20 93:6	152:20 158:22	38:25 121:13
250:19 252:10,17	61:12 78:12	94:16,17 108:14	173:7 176:19	227:19,21
257:16 258:21,24	100:12 113:19	108:25 109:1,6,24	186:8 230:11	separately
266:18,22,24	116:14 172:9	110:4 112:10,15	237:2,7,22,23	96:9 110:21 212:5
267:19 269:1	209:12 259:2	114:8 121:10	263:6 301:19	215:2
273:3 276:2	se	125:6 127:9 136:3	304:21	Serena
says	128:25 285:23	137:4 139:16	sees	6:22
45:13 62:5 70:7	search	140:6 147:16	167:4	series
77:18,21 85:11	51:21 52:1,1,3,8	150:7,13,14,22	select	166:23 209:25
90:16 99:21	184:8 291:20,22	151:21,24 153:12	258:7,10	serious
133:15 153:20	291:24	154:5 158:4,16	selected	184:20 306:10
156:3 169:25	searches	161:20,20 167:16	284:12	seriously
181:14 185:5	52:7	169:17 170:7,14	selection	142:11
203:1 207:15	searching	174:4,5 180:15,22	176:16 205:14	serous
274:4 276:16	120:16 256:24	181:13 184:7,19	sell	139:18 185:14
277:19 308:3	second	184:21 185:17,19	281:11	187:1,7 192:23
Schildkraut	85:2 90:9,12	186:14 194:24	Seminary	193:5 194:11
7:12 29:7,25 128:5	135:17 140:20,24	195:17 196:10	2:3	264:10 303:7,9
128:23 131:12	142:21 152:4	197:4 202:18	senior	SERVICES
234:3,12 237:8	185:5 187:2	203:2,8,9 204:2	21:12	1:24
238:19 239:5	210:13 219:17	205:6,22 208:24	sense	serving
240:15 284:19	224:8 238:6	210:22 213:13	119:16 296:25	11:5
school	260:24 270:4	216:3 218:16	297:1	set
288:17	276:17 277:5	221:16 223:23	sensitive	83:10 203:16 214:9
science	298:13 315:4	224:12 225:25	222:1,10,24 223:6	282:23
52:5 166:13 167:1	section	226:14,16 229:4	223:9,18,24	Setiawan
scientific	33:14 77:18 85:6	230:12 232:22	sent	30:1
56:11,25 57:2	92:4 108:14 170:9	233:16 235:4,11	24:6 42:1,2 291:16	setting
102:11 120:17	174:2 184:25	235:17 236:8	sentence	88:21 105:3,9
141:22 144:16,17	185:1 202:19	238:2,15 240:5,17	85:11 90:13 92:23	106:6,16 126:22
146:10,25 156:15	205:9 207:11,17	241:7 245:9,14	93:20 108:15	settled
156:21 157:14	228:5 240:18	246:13 249:25	109:24 110:3	97:12 161:23
181:9,11 199:17	244:8 264:18	251:18,25 253:23	135:9 140:25	seven
222:16 251:9	307:21	258:19 260:1,22	141:7,17 144:24	151:18 284:8
253:10,21 255:2	secure	262:7,16 264:2,19	167:19,24 169:16	SEYFARTH
300:12 305:22	283:14	264:23,24 265:3,6	170:19 171:21	3:13
313:23	see	270:12,13 272:21	180:22 185:2,5	SGO
scientist	11:7 19:5 21:16	275:8,22 284:23	186:10 210:14	149:9

shared 312:23 313:21	significant 10:19 94:1 110:23	150:8 214:22	145:5 245:9	sources 71:19 81:9
sharpened 239:15	131:20 132:3	246:8 263:3	247:19 249:1	South 3:18
SHAW 3:13	133:4,7,20 134:2	Sister 186:21 187:15	316:2,20	Southern 285:3
sheet 17:17,17 18:12	134:10,13,14	212:12 263:16	snapshot 101:18	space 17:23
318:6	135:2 136:15	sisters 199:24	social 25:19	span 262:15
SHKOLNIK 2:12	139:17 140:4	sit 289:20	societal 25:19	spanning 23:7
SHOOK 2:17	162:18 193:7	sitting 11:23 18:22 40:4	sole 124:6 312:16	speak 60:20
short 259:11	226:25 235:18	243:3 295:14	solely 66:3	speaking 29:13 30:25 90:4
shortly 164:5	236:9,22,25 237:5	situation 24:7 106:24 162:6	solid 154:17	110:18
show 134:13 175:6	259:23 264:12	183:12 222:7	somewhat 66:1 113:3 282:21	specific 48:8 75:10 107:8
262:24 313:10	265:9,12,13	224:8 228:11	Sonal 44:7	128:22 136:25
showed 88:11 193:3 312:6	266:10 267:1	situations 221:18	Sophie 1:21 100:5,15	172:24 197:18
showing 92:25 114:16	268:13 269:1	Sixteen 6:16	320:3,22	199:8 214:1
236:15 263:7	271:3 272:18	size 136:17 140:2	sorry 11:16 14:22 15:17	233:24 256:21
264:5	273:5 274:20	187:17 200:2	16:21 20:13,16	295:15 316:23
shown 125:21 138:5 168:2	276:19 277:9	sizes 237:3	39:3 56:13 69:23	specifically 11:25 21:25 24:11
173:18	278:9,20 279:4	sjames@shb.com 2:19	91:10 110:2	41:10 44:10 50:24
shy 167:14	significantly 187:6	slight 203:20	111:18 114:3	54:22 70:23 71:11
sic 76:25 99:12	signing 18:12	small 104:8 107:15	115:23 116:14,19	72:4 74:20 75:8,9
side 18:9 78:14 240:2	similar 25:4 60:5 142:25	136:17 140:2	118:3 146:15,16	76:19 79:24 80:4
sides 69:19 70:9,10	143:9 168:3	181:14 250:10,18	146:17 148:2	83:13 86:23 94:7
Siemiatycki 44:6 174:20 290:21	178:11 213:6	250:21 251:2	154:5 165:16	95:4 107:5 119:3
signature 18:10 317:9 318:10	214:23 226:4	smaller 199:22 237:3 251:6	187:9 192:3 209:2	119:9 124:2,3
signed 17:18 318:7	229:13 245:14	303:14	237:11 239:25	130:23 139:2
significance 62:17 135:9 215:10	246:14 250:3	Smith 3:23	249:23 266:8,13	140:9,12 153:2
237:4 263:21	251:23 253:6,12	Smith-Bindman 44:7	268:16 276:25	160:18 163:15
274:24	253:18 256:4,6,24	smoke 259:24 260:7	284:10 288:4	171:8 172:15,16
	257:12,14,18	smoking 141:12,23 142:3,12	305:24	175:10 177:4
	258:7,13	142:21,24 143:10	sort 35:6 108:16 124:17	178:25 187:16
	similarities 143:7 155:1	143:13,21 144:17	177:19 206:9,20	191:7,11 194:16
	similarly 225:4		260:14	212:11 220:25
	simple 52:2		sorts 103:8	224:7 230:19
	simply 47:25		source 110:15 117:20	244:18 246:22
	Singh 44:7 291:5,8		158:22	252:14 286:13
	Singh's 291:11			293:4 303:23
	single 17:13 24:4 59:5,16			specifications 83:1,5,10,14,18,20

83:24 282:4	265:23 270:4	237:5 264:11	strike	111:17,19 125:23
spectrum	271:22 320:1	265:9,12,13	69:10 122:11	127:10 130:22
305:8,14	stated	266:10 267:1,15	206:21 311:7	131:10 140:18
speeches	54:13 70:12 81:7	268:12,25 274:20	strong	142:5 143:5,11
30:20	83:23 90:17 91:6	status	144:2 223:3 245:16	154:10 155:1,6,11
speed	95:23 109:7	10:9 178:7 203:25	246:10,12,15	156:23 158:25
165:19	172:23 181:15	stay	248:23 249:7,11	159:9,12,19,22
spend	193:17 207:2,3	221:7	249:17,18,20,20	160:3 161:6 162:1
71:25	261:16 268:21	Steering	251:11 257:3,17	162:2,5,11,12
spent	279:3 303:21	4:18 8:21 36:18	258:1,19 261:14	164:4,14 170:24
313:2	307:6	Steve	261:15 287:11	171:11,13 176:20
spoken	statement	2:9 8:22 12:11	288:23	184:10 185:7,12
237:24	39:16 69:5 70:14	steve.faries@mu...	stronger	185:21 186:8,13
spring	70:16 71:17,21	2:10	143:14,20 208:11	186:16,18 187:1,5
166:12	81:12,13 101:23	sticker	228:25 230:13	187:7,8 188:3,9
stand	134:3 147:3 149:6	77:9	231:14 261:22	188:13,18 190:18
18:16	149:22 150:3,7,8	stickers	301:2,5 302:2	191:3 192:5,8
standard	150:15 158:1,19	173:15 175:18	strongest	193:19 194:8,25
224:22 225:1	170:10 172:9	stop	143:22 158:3,20	195:20,21,22
278:23 288:10,22	181:13 201:18	201:22 308:13	159:7 207:7	196:22,23 197:7,8
standards	202:11 204:5	story	210:16,25 211:8	197:13,14 198:2,2
51:21 67:2,4 282:3	215:8,21 222:14	69:19 70:9,11	strongly	198:4,4,16,18,21
stands	222:15,16 225:10	stratify	51:18 90:21 92:16	198:22,24 199:9
26:9	239:12 241:1,2	236:23 237:2	302:3 316:2	199:12,13,19,20
start	269:18 277:24	Street	structure	199:22 200:6
36:6 38:8 87:25	278:19 279:15	1:17 2:8,17 3:13	26:11	202:6,7 203:19
133:2 218:8	statements	strength	structured	205:11,15 207:13
started	30:25 39:11,19	244:8,11,15 245:2	93:13	207:21 208:18,22
208:7 218:10,17	71:7 129:3 130:11	245:4,10,20 246:5	structures	209:5 211:7,20
220:8	279:12,13	250:3,7 253:5,11	77:23	212:10,24 213:5,8
starting	states	253:15 256:3	structuring	213:9 214:14,15
140:21	1:1 92:11 94:4,9,23	257:15 258:6	31:5	215:11,13,15,18
starts	244:20	261:3,10	student	216:7,17 220:2,6
90:13	stating	strengthened	28:24,25	220:20 222:15,18
state	259:21	102:22	students	222:20 223:13
9:15 15:20 50:4	statistical	strengthens	288:19	224:21 225:5
90:12 98:24	135:9 200:2 213:3	98:3,13,13 102:7	studies	226:12,21,21
102:14 108:17	215:10,12 237:4	strengths	6:16 7:7 34:25	227:1,14,14,19,21
129:4 131:19	263:21 274:24	126:14 197:16,18	52:24 53:2,5,8,11	228:3,13,14,19,20
140:20 141:6	284:19	198:17,20,21	58:1,11,20,24	228:22 229:1,4,5
146:3 167:24	statistically	301:6,8,13 302:4	60:3,7,11,25 62:2	229:11,12 230:1,2
169:11 174:6	131:20 132:3 133:4	stress	62:3,13 63:4,4,5	230:8,10,14,14,18
180:17 205:7,9	133:7,20 134:2,9	226:2	88:25 89:7,16,19	230:18,20,21
207:19 212:21	134:14,21 135:2	stressing	89:24,24 90:1,22	231:15,19,21,24
222:6,12 224:22	136:14 139:17	208:1	90:24 92:17,25	232:14 233:10,13
226:19,24 240:19	140:4 193:7	strictly	93:15,25 104:3,8	237:1 238:11
252:6,9,10 265:7	235:18 236:25	157:4	104:18 106:24	241:11 243:17

260:15,15 262:11 262:22,23 263:15 264:3,11,13 266:20,20 267:4,5 267:17 268:1,7,10 268:19,20,24,25 270:10,11,16,17 270:18,20,25 272:9,13,24 273:1 273:4,7,8,22 275:4 281:16 284:5,8,9,12,16 284:21,25 286:7 286:11,23 298:24 299:7,8,13 300:19 300:20 301:7,8,12 301:22,23 303:4,6 303:10,22 304:4 304:14 309:16,17	199:24 200:4,6,9 202:13,20 203:6 204:17 206:5,23 206:23 208:6,7,12 209:4,4,8,10,24 210:15,16,25,25 211:4,5,8 212:12 212:13 217:9,15 217:24 218:1,15 219:11 221:4 223:10 224:10,10 224:16,17 225:6 225:14,15,19,21 226:8 227:2 229:6 229:10 230:25 231:1,8 236:17 238:9,19,21,24,25 240:15 241:18 246:8 263:3,6,11 263:16,18,19 264:4,4,15,18 266:23 267:9,11 268:14 269:7,15 270:20,23 271:1,2 273:9 275:5 283:3 283:4,6,8,10,15 284:2,3,17,20,22 284:24 285:1,3,5 285:5,6,13,17 286:18 292:12,14 299:19 300:24 301:3,5 302:1,2 312:6,7,10,12,18	15:23,24 16:18,20 26:18,19 27:23 28:6 30:13 79:4 85:17 283:18 293:19,22 subsequently 23:24 subset 138:4 substance 13:11 30:13 substances 120:14 121:5 297:18 substantially 45:20 substantiating 119:6 subtype 207:23 303:7 316:23,24 subtypes 187:6 210:20 303:2 303:3,6,9,11,12 303:13,16 310:16 310:21,24,25 311:3 315:19,20 316:4,7,9,18 sudden 12:12 sufficiency 83:4 sufficient 101:1,19 102:14 169:6 174:15 176:1 178:8,18 254:18 255:3 301:1 303:1 304:1 304:8,15 suggest 69:25 70:13 87:9 108:20 183:1 257:9 296:15 suggested 132:21 suggesting 142:22 227:1	suggestion 161:14 suggestive 185:15 Suite 2:12,17 3:3 Suites 1:17 summaries 159:5 summarized 154:11,13 summarizing 147:22 summary 148:9 161:23 162:4 229:21 235:16 summer 11:19 291:25 Super 9:15 superior 190:14 197:2 198:7 198:8,25 supervision 320:9 supplemented 56:18 supplier 80:15 suppliers 79:3 supplies 281:8,19 support 39:11,15 66:12,15 66:21 67:8 72:1 92:24 93:19 101:19 141:17 142:23 143:18 144:24 145:14 155:6,9 169:6 170:11,25 176:1 176:12 178:6 186:16 222:15 224:4 225:10 231:18 258:1,6,13	303:1 supported 39:19 51:14 108:24 277:24 supporting 168:17 205:12 254:20 supports 71:21 123:9 sure 12:23 16:3 25:2 34:21 35:18 36:7 41:25 42:1 52:13 55:7 59:5 61:13 64:12 77:14 87:17 87:21 100:12,14 101:4 107:11 111:19 113:15 125:10 142:20 143:19 144:9 145:12 165:20 173:22 188:1,20 194:18 209:21 215:7 217:16 225:13 237:9 243:12 254:24 255:10 258:15,16 259:9,11 269:9 276:15 277:25 280:5,7 288:5,7 292:1 297:3 305:24 314:18 surprise 46:11 47:20 50:10 74:6,21 surprised 45:24 112:14 surprising 51:17,19 237:6 surrogate 300:5 surrounding 156:16,22 survey 77:19,22 survivors 25:21
study 7:4,8,12 20:22 29:2 29:3,5,8,18,24 58:6,16 59:2,5,8 59:16 60:9 61:6 104:4 105:5 106:23 107:3 125:5,6 128:5,10 128:16,19,23,24 129:4 130:7,7,11 130:15,16 131:12 131:19 132:20 134:5,22 135:19 135:22,25 137:1 138:3,6,15,15,16 138:17,20 139:4,5 140:13 164:23 166:18 169:21 184:3,10 186:20 186:21,22,23 187:13,15,15 188:3,11,19 189:23 191:17,23 192:9,13,20 193:3 193:21,24 194:3 195:4,14 196:8,10 196:14 197:1 198:13,23 199:6,6	study's 221:19 studying 197:15 sub 173:14 subject 18:19 238:13 subjective 206:9 subjects 6:15 113:2 224:10 224:17 225:15 submitted			

swear 8:8	259:15 272:3 309:25 320:8	146:3,11 147:1,18 147:25 148:2	talc/ovarian 188:25 189:5,9,15	talked 50:24 167:8 195:10 206:18 234:16 269:3 282:14 290:7,10 295:1 296:14
switch 175:18 280:9	takes 172:2	149:4,9,23 150:24 151:25 154:21,25 155:3,10,15,17,24 156:19 157:9 158:12 160:19 161:11 162:6 166:6,20 168:1,4 174:11 176:14 185:13 186:19 187:14,17 188:14 190:13 196:24 197:7,8,20 199:11 201:12 205:20 208:8 209:5 210:19 212:10 213:2 217:14 218:21 220:5,7 222:8 224:3,18 226:4,17 227:16 228:11,17 229:24 230:21 231:7 232:7,11 233:13 233:22 234:23 235:23 236:4,17 245:11,15,21 246:8,24 247:7 251:10 252:25 253:11,25 254:8 254:16 255:8 259:22 263:25 266:4,20 270:7 271:25 272:17,20 280:16,21,24 281:8,18,24 282:4 286:2,9,10,15 292:12,15,16 295:2,6,11 296:6 297:18,20 298:1,9 298:15,18 299:9 299:14,23,25 300:7 304:9 305:10 310:11 313:15 315:16	talcum 1:6 52:2 63:25 64:4 64:8,19 65:3,18 66:7,13 68:20,25 68:25 69:7,9 70:13,15,18,19 71:1 75:6,18,23 76:2,5,9,14 79:20 79:22,24 80:1 81:10,14,22 82:14 83:2,9 84:3 86:1 86:10,22,24 87:4 87:6,8,11 88:2,6 88:11,14,16,21 93:11 94:6,20 96:10 102:12,14 105:11,22 106:8 106:13 109:19 111:12 112:7 113:21,24 114:7,9 114:13,14,17 116:3,4 117:8,13 117:16,22,24 118:6,7,19 119:16 119:22 120:3,25 121:5,9,14,16,24 122:3 123:5,23 124:20,23 125:4,7 125:13,19 126:5 126:22 129:10 140:9 150:11 154:21 223:17 281:9,12,16 285:18 291:21 292:4,6,7 294:24 296:1,3 303:19,24 304:1,4,23 310:12 311:6,8 312:2,4 312:22 313:9 314:6,14 319:2	talking 37:10 50:1 94:19 96:11 101:10 104:12 106:12,13 174:17 181:10 215:12 265:25 282:9,10,15 286:6 287:10 294:5 299:13 300:15 313:2 315:25
Switching 289:4	talc 3:2 5:6,20 6:6,9,12 6:14 7:4,16,21 8:14,16 9:18,25 10:24 11:3,6,8,9 11:20,21,25 12:7 12:17 16:9,13,15 17:3 19:10,15,17 19:18 20:23 21:6 21:9,15 25:11 26:1,14,21,24 27:5,13,16 28:10 28:13 30:7,10,21 31:1,23 48:15 52:2,9,24 53:2,5,8 53:11 56:20 58:2 58:11,17,20,24 59:3 60:3,25 61:6 62:21 63:25 66:1 71:18,20,22 76:25 77:25 78:1 79:3 79:11 80:16 94:11 96:3,11,20 97:12 97:13 98:14,17 99:12 100:22,23 101:18 102:8,23 103:2 111:23 112:8,11,18 115:9 115:21 116:6,9,12 117:6,11,16,22 118:6,18,24,25 119:6,23 120:18 121:10 123:7 126:2,18 128:10 128:17,25 129:4 129:17,21,25 130:5,8,12,24 131:8,20 133:3 135:23 136:1,13 139:12,24 140:7 140:12 142:14 143:1,14,24 144:18 145:8	talc-containing 79:11 85:15	talk 51:25 111:18 164:16 181:16 182:5 216:5,6 244:2 289:4	talks 263:10 taught 288:18 teaching 10:13,18,20 243:24 team 254:2 teams 262:12 Tecum 4:16,20 teens 218:10 teleconferences 13:3,4,7 telephone 2:4,9,13,18,23 3:4 3:9,14,19 25:7 tell 21:2 31:11 34:19 43:10 70:24 75:19 116:10 137:16 175:5 194:15 225:5,12 240:3 282:9 308:14 telling 71:4 224:1 225:7 tells 22:25 265:11 ten
sworn 320:7				
sworn/affirmed 9:3				
synonymous 182:8				
syntheses 92:4				
system 103:8				
systematic 5:12 6:7 7:19 66:14 66:22 127:3,10 254:3 293:12,13 314:3				
T				
T 319:1 320:1,1				
table 137:5,5 139:11 187:4 235:4 236:1 236:3,8 266:9 273:25 274:1,3,8				
Taher 7:21 306:18,20,24 307:4,9 312:6,10 312:12,18				
take 14:3,4 25:1 40:13 52:11 61:14 113:10,16 163:5 163:19 164:4 165:5 173:20 199:23 209:25 239:1 277:22 305:14 309:15				
taken 1:16 34:8 52:17 115:4 150:22 165:10 211:15				

29:4 72:11,11 136:5 189:15,23 193:12,16 209:13 216:14 tended 303:11 tendency 166:25 tenfold 247:21 Teniola 28:24 term 52:8 62:17,18 193:2 terminology 115:13 134:10 183:1 197:10 246:4 249:10 250:11,12,13,16 287:6 288:8 300:14 terms 51:21 52:1 86:16 89:3 155:7 184:8 263:20,22 267:8 288:23 294:4 300:17 316:16 Terry 6:20 139:4 140:17 179:18,21 180:6 276:10 test 80:3 83:21 274:18 274:23 275:10,25 276:6 279:18,20 tested 75:11 79:5 80:6,15 testified 9:4,21 59:18 62:20 99:6 103:20 291:7 291:20 testify 289:14 testifying 22:5 168:16 testimony	17:6,9,10 18:7,13 18:16,24 61:2 69:21 98:10,20,24 98:25 99:17,21 101:9,11 115:19 119:20,20 198:6 268:9,14,18,20,21 281:14 286:9 310:19 318:4,5 320:6,7,11 testing 53:14 76:13,25 118:11 121:19 127:12,14 Texas 2:8,18 3:4 text 180:14 275:20 textbook 288:19,20 textbooks 288:11,14,23,25 thank 20:17 28:19 29:22 33:4 36:8,21 38:1 38:5 55:12 73:15 77:4,8 78:15 84:18,25 91:20,20 91:23 100:9,13,15 100:18 113:19 115:1 131:23 151:14 186:2 196:5 202:16 210:5 211:12 259:12 271:11 294:12 302:11 308:17 309:18 314:23 317:1,4 theoretically 221:12 therapeutic 7:7 227:8 229:12 thereof 320:16 thing 34:6 44:18 232:13 278:23	things 35:3,5 52:6 104:6 126:19 129:17,21 141:18 154:14 164:11 165:20 182:4 183:9 184:8 186:5 190:23 222:20,22,24 223:8 282:14 289:5 292:25 305:2 think 16:5 18:25 20:12 22:8,12 24:7,20 41:10,21 46:16,23 46:25 47:4,9,12 48:11,12,15,24 49:16,19 50:9,24 51:19 54:17 55:22 56:14,15 57:17 58:15,23 61:4,5 62:7,10 65:20 67:7,16 70:6,10 70:12,16 71:5,6 71:16 72:6 75:11 76:19 77:15 80:18 81:3,13,15,23 82:8 89:16 90:8 95:7,9,20 96:15 97:22,23 98:3 101:22 102:5,7,17 102:19,21 103:3,6 111:4 113:14 114:21 119:21 124:1 125:18 127:1,24 129:7 130:21 134:3,25 136:4 139:2 141:25 143:9,25 144:21 145:7,13 146:21 148:2,9 150:17 151:2 153:2 155:14 158:21 161:19 162:22,22 163:10 164:21 167:3,4 171:9 172:13	178:19 179:2,2 180:8 181:4,8 182:7 183:4 185:1 190:12 192:12 197:10,13 198:19 199:5 200:13 201:16,19 202:3,4 204:10 206:8,10 211:6 214:11 215:8,9,13,23 218:3 223:5 225:7 226:1 228:21 229:20,20 230:5 230:15,21 231:18 231:24 232:9 234:7 238:20 239:4,6,10,20 240:1,8 241:10,16 241:20,21,25 242:4,23 244:22 244:24 245:4,5,10 245:15,17,20 246:4,5,11,14 247:10 248:3,4,13 249:3,12,24 250:24 251:5 252:5 255:6 257:2 257:16,17 258:18 260:6 261:12,16 262:5,20 263:23 264:5 266:7 267:7 270:14 271:13,14 272:8 275:11,23 276:5,7 279:3,5 279:16,17,21,23 282:16 283:8 285:7 286:4,6,24 287:19 290:25 291:18 293:7 295:1,13,18 297:11 300:2,14 300:15 301:1 302:14 304:3,12 304:13 306:9 309:5 313:10,25 316:12,21 thinking	95:20 151:22 167:5 181:17 225:18 third 94:8 121:20 157:25 232:19 275:1 thorough 242:23 thoroughly 243:8 255:11 thought 44:25 48:17 114:3 142:8,10 164:13 209:10 219:14 224:25 225:1,24 226:2 286:9 thoughtful 242:24 thoughtfully 240:10 threat 221:19,24 232:20 243:17 three 24:14 55:2 104:14 186:18 202:6 216:17 221:18,22 232:25 243:9,11 243:15,16,18,20 263:15 three-fourths 108:17 thumb 33:21 time 8:4 11:17 27:23 33:11 40:13 47:17 48:1 52:11 79:21 95:11 97:15 98:2 101:1,19 102:19 102:21,22 113:23 114:7 116:9 132:10,11 143:5 143:12 145:22 147:14 154:11 160:21 162:2 163:21 165:4 172:2,4 178:13,17
--	--	---	---	--

179:1,5,11 189:20 191:17,25 200:22 201:10 211:9 220:5,8,12 225:15 237:13 240:21 264:25 280:3,19 283:11 289:12 291:19,23 292:9 294:2 295:7,15 301:1 307:9,19 309:19 313:2 317:2,6 times 40:21 52:3 60:15 82:6 151:18 158:23 166:19 169:13 183:17,20 199:3 200:22 206:24 207:4 240:18 253:2 273:23 274:4,17 301:10 314:5 timing 177:21 tipping 178:14 Tisi 13:3,7 title 20:20 45:5 titled 5:8,11,14,17 6:3,6 6:9,11,14,18,21 7:3,6,10,13,16,19 39:1 244:8 today 10:25 11:3,23 12:15 13:22 16:10 18:17,22 33:25 35:8 37:11 38:13 40:4 43:7 55:23 56:3 60:23 155:24 168:16 201:10 206:17 216:13 243:3 253:2 263:2 265:25 267:3 268:18 269:3	281:14 287:5 289:7 291:7,17 292:23 294:6 295:14 297:12,17 298:2 300:11 301:11 305:17 308:6 313:2,21 314:5 today's 8:3 12:6 19:2 34:18 38:10 told 14:6 31:19 Tolu 28:24 top 89:5 90:12 103:16 128:3 140:21 159:1 167:16,23 180:17 203:3 212:20 232:25 246:11 252:21 253:8 257:25 259:20 topic 56:9,12 64:25 65:12,17,22 66:24 67:18 82:3 199:15 200:18 201:14 202:8 206:1 208:2 221:6 223:19 234:1 250:5 topic.' 222:10 topics 48:8 223:1 260:19 289:4 total 212:25 272:16 284:8 totality 313:6 touch 12:3 303:17 touched 215:25 234:15 Trabert	7:15 237:7,15,25 238:3,7 Trabert's 238:17 Traci 29:25 track 180:8 traffic 24:16,22,25 trained 54:18 training 57:19,20 transcribed 320:9 transcript 4:12 5:4 17:14 19:4 19:6 40:1 54:24 56:7 61:9,20 77:7 transcription 318:5 320:11 transcripts 291:4 transition 10:16 282:17 transitioned 178:7 transitioning 221:6 translate 302:10 translocation 94:12 Travis 2:17 treat 32:12 316:16,18 trend 274:19,23 275:11 275:25 276:7,19 277:9 278:16,20 278:22 279:1,4,18 279:20 trends 271:24 272:19 273:5	trial 166:22 tried 59:11 293:16 trigger 239:21 240:13 true 18:13 70:17 122:21 125:25 141:25 145:7 201:18 203:22 220:20 305:2 318:4 320:10 Truls 31:16 truth 194:4 truthful 62:6 try 70:3 245:25 284:14 trying 15:17 48:11 67:8 69:25 71:5,17 75:9 127:1,7 158:21 181:10 212:11 228:21 230:6 256:10 257:2 258:18 275:21 283:13 289:1 293:8 Tube 6:3 151:10 tubes 298:19,24 299:10 299:15,23 300:8 TUCKER 3:18 turn 33:13 38:20,24 85:2 91:25 94:5 139:10 147:8 151:16 153:15 194:18,23 206:22 209:23 210:7,8 222:4 251:14 264:14 298:14	turning 119:10 122:10 212:19 twenties 218:11 two 24:14 50:11 55:2 104:14 136:10,21 139:7 141:21 142:20 144:22,23 149:25 160:23 164:25 173:11 175:21 180:9 187:5 188:13,18 188:24 190:18 202:14 227:5 230:25 231:1 234:13 237:18 244:20 260:18,18 263:14 273:19 274:21 307:11,17 type 86:9,21 112:6 221:4 243:24 270:11,16 313:21 313:21 types 35:5 82:23 86:13 86:15,24 120:7 121:3 130:23 144:23 287:5 311:12,15 typical 22:15 27:23 166:9 typically 89:23 157:5 163:10 302:1 <hr/> U <hr/> unaware 224:6 233:25 UNC 290:4 unclear 11:11 12:1,5 uncomfortable 223:14
--	--	---	---	---

uncommon 263:3	188:4 190:17,19 213:3	185:13 186:19 202:22 205:20	version 6:5 130:3 151:12 153:13 154:1,4,6 154:22	walk 221:22
uncontrolled 176:17 177:5	unfeasible 299:18	209:16 210:20 217:14,20 220:5,7 220:15 222:8	versus 101:24 102:2 104:12,15 131:8,8 155:15 198:24 215:15 236:13	walked 243:14,18
underestimate 160:12 171:14	unfortunately 55:2 151:17	223:17 224:3 239:16,17 246:2 254:1 265:19 266:4,11 267:10 267:22 270:7 274:4,21 275:7,7 275:16 276:3,13 277:19 278:16 281:8 288:11,19 288:23 289:1 290:23 293:11 298:9 299:17 305:10	Video 36:19	want 36:6,14 38:12 65:8 75:13 77:4 89:6 99:9 100:11,12 101:6 105:3 113:5 113:8 116:15 146:7 159:3 161:21 172:10 209:14 222:25 246:13 255:10 277:23 289:4 298:5 305:24
underlying 128:24 159:8,12,19 160:3	UNITED 1:1	users 113:24 114:9,16 130:8 131:21 133:3 218:21 276:18 277:8 279:15	VIDEOGRAPH... 3:22 8:2 52:15,18 115:2,5 116:20,23 165:8,11 211:13 211:16 219:20,22 259:13,16 278:2,5 280:10,13 302:16 302:19 308:16 309:23 310:1 315:2,6,9 317:5	wanted 12:23 19:6 24:12 51:17 153:10,12
understand 9:13 11:2 12:2 14:12 33:9 42:7 46:3 48:2,4 57:8 62:16,18,19 65:1 66:5 69:17 70:7 70:21,25 71:13 73:6,9,21 74:17 74:22,24 80:14 96:9 103:7,13 108:6 124:9,14,16 125:10 129:13 131:5 134:7 144:7 147:12 153:14 180:18 192:22 246:16 248:18 263:9 280:21 281:7,11 299:4 300:18 305:18 306:2,16,20,24	universe 256:16		videotaped 1:11 4:15,19 8:5	wants 100:7
	University 10:10 285:2		view 148:13	warning 84:3
	unrelated 253:7,13		viewed 223:18	warranted 21:18 207:24
	unusual 46:16 141:1		viewpoints 246:4 258:23	washed 192:24 193:1
	up-to-date 183:25		Virginia 2:4	Washington 3:14
	update 189:19		virtually 233:11 263:6	wasn't 99:16 148:17 166:21 276:25
	updated 20:4 33:19 153:20 208:9 292:1		vis-à-vis 312:1	way 15:22 17:22 20:15 23:19 31:5 39:24 40:4 43:6,13 59:24 93:13 95:8 105:14 108:17 126:9 133:22 137:13 139:16 147:9 153:22 162:20,23 166:9 180:25 193:25 206:13 208:11 211:4 217:22 229:16 251:13 256:9 261:16
	updating 190:9 220:1		V	
	usable 226:1	validity 221:20		
	usage 218:2 219:13 235:24 236:4,6,10 236:17 292:4	Valley 7:17		
	use 5:20 6:6,9,12,18,22 7:4,11,20 76:3 87:4 96:11,20 97:13 98:17 101:18 126:5 127:3 128:11,17 129:10,10 130:12 130:17,23,24 131:17 132:1 134:11 136:13 139:13,24 140:7 140:12 143:25 149:4,23 154:21 166:15,25 168:1,4 174:10 182:4	value 124:7 289:2		
understanding 15:10,19 43:24 181:11 193:22 228:10 281:4,10 281:13 296:11 305:21 306:6,12 311:25 312:3 314:10,11		values 134:21		
Understood 11:15 216:19 277:3		variety 126:18 129:14 226:20 229:6		
undertake 111:7 131:13 182:19 233:21		various 12:4 161:10,10 251:7 313:3,14 316:9		
undertaken 64:2		vast 233:10 303:7,8		
undertook 82:2		verbal 13:25 14:1		
unexposed		verify 132:7		
			W	
			W 2:8 3:20	
			Wacker 3:18	
			wait 34:11 167:20 186:1	

263:13 279:17,19 293:1,5 300:6 ways 160:25 225:16 we'll 13:22 14:7 25:1 35:15 36:7 37:10 78:14 113:15 116:16,18 173:14 175:18 209:25 232:18 we're 10:25 17:22 18:2 29:16 33:11 69:6 90:4 91:15 95:7 95:17 96:11 104:12 106:12,13 113:6 130:14 131:22 164:4 167:8 208:14 223:11 224:23,24 225:6 266:11 273:25 293:10 308:14,15 we've 9:10 50:24 52:12 128:21 146:13 156:10 206:16 207:17 209:12 215:25 231:10 236:23 259:7 263:15 294:5 weak 246:19,25 248:17 248:22 249:7,10 250:10,18,21 287:10,15,17,22 288:6,23 weakened 211:5 weaker 193:3 247:16,17,18 247:19 weaknesses 126:14 164:16 197:16,18 198:17 198:20,21 301:9	301:10,12 302:4 website 5:20 155:24 week 42:6 188:5 291:14 307:11 weeks 19:3,5 weigh 141:2,18 144:12 weighed 164:13 weight 145:2 weighted 142:4 weighting 244:25 welcome 84:19 well-accepted 197:14 199:6 245:13 251:21 279:19 well-established 197:14 245:7 well-known 290:22 well-respected 174:21 179:12 Wendy 30:1 went 122:4 164:12 192:12,20 193:20 194:3 218:9,13 241:20 242:3,15 253:15 289:23 Wera 6:10 whatsoever 187:14 When's 145:22 WHI 202:13,20 217:8,13 217:13 219:7	white 5:15 27:16 135:14 136:8,13,18 137:4 wholly 108:24 wide 229:6 witness 8:8 10:23 13:2 20:16,18 22:21 23:2 26:24 27:8 29:18 31:21 33:4 41:6 42:9,19 45:24 46:9,15 47:20 48:4,24 49:6 50:14,21 51:25 54:12 55:21 57:16 58:4,14 59:11 60:16 61:4 62:10,24 63:13 64:6 65:7,20 66:20 67:7 68:7 68:23 69:23 70:6 71:16 72:18,25 73:9 74:11 75:1 76:8 78:23 80:24 81:7,21 82:7,20 83:13,23 84:10 86:3 87:17 88:5 89:3,13,22 91:8 93:17,22 94:23 95:4 96:6,17 97:15,22 98:11,21 101:4,22 102:17 104:2,25 107:8 108:10 109:6 110:8 111:1 112:14 113:11,17 114:1,21,25 116:2 118:3,17 119:2,21 120:21 122:7,15 123:11 124:1 125:2,18 126:4 127:18,24 129:7 130:19 131:15 132:5 133:6,12 134:19 135:7	136:12 137:10 142:17 144:5,21 145:12 148:16 149:12,19 151:14 153:7 157:18 160:8 161:3,19 162:15,22 163:18 164:24 165:4,7 167:11 168:12 170:5 171:8 172:13,23 174:20 175:1,10 176:7 177:2,15 178:10 179:10 180:3 181:4 182:14 184:5,19 186:4 188:17 189:18 190:1,7,16 192:17 193:1,15 194:6,15 195:25 196:13,18 197:24 199:4,18 200:21 201:4,16 201:18,23 202:2 202:16 204:16,23 206:3,13 207:2 208:5 209:16,19 211:11 213:23 214:5 228:16 229:19 230:5 234:20 236:12 241:16 242:15 246:1,21 247:4 248:3,12 250:24 251:5 255:18 258:15 266:6 267:7,19 268:16 271:9,12 274:12 276:25 277:22 278:7 281:21 287:25 294:13 295:18 296:9,24 297:8 298:6 299:2 299:12 300:2,23 301:25 302:13 304:12 305:21 306:6 307:4 309:4 309:13,20 313:25	316:12 317:3 319:3 witness(es) 320:5,7,11 woman 223:10 224:1 women 5:15 20:22 26:9 27:11,12,16 90:22 90:24 92:17,25 128:13 132:10 135:14 136:9,13 136:14,17,18 137:4 181:23 188:4 190:18 205:21 208:6 218:6,10,17,18 220:16 222:24 223:4,7,14 225:4 225:22 226:2 240:21 284:15 287:1 296:4,10 297:21 300:8,25 305:7,14 Women's 186:22 285:1,4 wonderful 208:11 word 108:16 162:19 163:13,19 166:15 166:25 167:15 181:19 wording 24:11 38:18 133:17 241:9 words 66:18 275:3 287:22 288:9 work 10:12,20,23 15:8,9 15:16 16:9,11,23 21:14 28:23 31:13 31:14,18 34:22 37:5,6 48:12,13 48:16 53:22 54:15 78:14 112:6 124:7
--	---	--	---	--

126:12 152:21 180:18 181:9 290:14 292:9 314:1 work-in-progress 29:11,17 30:5 workday 105:20 worked 12:18 13:12,16 29:3 285:16 working 13:18 16:24 22:4 26:4 28:10,25 30:11 31:21,22 34:16,19 35:25 78:14 92:12 173:3 works 28:9 30:9 78:11,13 world 231:8 232:7 250:17 worried 231:4 worries 77:10 277:3 wouldn't 68:17 71:12 72:3 101:7 112:14 113:23 114:8 183:11 197:11 211:7 250:20 281:17 299:5 write 38:15 167:18 293:17 writing 28:3 65:24 66:2 239:5 writings 32:7 written 24:2 25:4 27:25 28:1 31:25 32:6 95:11 110:4 133:13,15 150:20 157:3 247:14 wrong	22:23 90:9 120:10 144:19 196:6 227:11 wrote 39:12 42:21 <hr/> X <hr/> X 1:3,10 <hr/> Y <hr/> yeah 26:17 49:19 113:17 118:8 146:23 150:19 153:23 159:16 162:15 191:10 229:19 258:5 259:7,12 260:24 275:23 year 10:18 110:11 217:21 282:24 295:15 years 23:7 29:4 41:7 54:16 85:18 136:5 142:2 177:3 189:15,23 191:9 193:12,16 208:10 216:10,14,25 217:4,10,22,25 218:7,14 222:18 222:18 224:21 288:17 295:23 299:17 300:9 yes-or-no 156:14 172:6 175:4 York 2:13 <hr/> Z <hr/> Zambelli-Weiner 44:5 <hr/> 0 <hr/> 051 274:19	07932-1047 2:22 07962 3:8 <hr/> 1 <hr/> 1 4:10 5:7 15:2,3,5 15:15 16:10,19 97:4 103:9 133:25 134:6,7,7 137:10 137:12,19,20 138:7,11,15 139:20 155:12 252:12,18 258:8 262:25 263:7 267:12,15 268:1,2 268:3,7,24 1.04 136:19 137:3,7,20 137:23 138:6,10 1.06 264:22 265:8,16 274:13 1.12 264:5 1.13 266:13 1.14 266:13 1.15 139:17 1.19 133:25 136:18 235:18 264:6 1.2 158:15 242:12 255:15 256:19 257:23 1.25 213:6 257:7 1.3 242:12 255:15 256:19 257:7,23 266:12 1.4 266:12	1.5 158:15 1:48 165:9,10 10 5:3 49:10,12,16 50:1 157:22 217:4 247:12 10:05 52:16,17 10:18 52:17,19 100 5:9 59:15 60:11 100C 91:16,19 101 182:15 107 5:11 11 5:4 61:15,17,21 76:24 77:7 140:19 244:1,7 11,933 6:15 11:45 115:3,4 11747 2:13 119 25:18 12 5:5,6 55:10 77:2,6 251:14,20 253:20 255:1 270:23 12.4 217:10,25 12:39 115:4,6 12:40 116:21 12:41 116:24 120 21:4 121	25:14 1294 108:13 13 5:7 50:17 51:8 84:16,20 259:19 260:8 136 5:14 139 5:17 14 5:8 21:4 55:11 91:14,17,21 183:17 191:9 206:24 216:10,25 259:19,20 260:20 262:5,5 14-year 191:23 193:10 1414 235:2 1416 240:5 149 5:20 15 4:10 5:11 107:22 107:23 259:6,8 151 6:3 1510 3:3 154 199:25 16 5:14 61:24 136:7 136:11 177:3 16-2738 1:7 319:4 165 6:6 169 6:9 17 4:11 5:17 61:21 139:6,8
--	--	--	---	--

173	162:8	4:25 5:5 10:6,9	7:10	4:5
6:11	2003	17:7 19:9 30:22	237	2A
175	175:14,17 177:9	45:13 46:13 47:2	7:13	97:7 103:9
6:13	2008	47:17,24 48:6,20	24	2B
18	174:13 178:1,2,5	49:3 50:18 51:11	6:18 166:7 180:6,7	96:12,21 97:10,12
5:20 149:22,24	179:1	153:20 162:8,10	276:15	100:23 101:2,18
180	200834000001	2019	248	101:19,20 103:3,9
6:18	320:23	1:14 8:3 143:1	169:16	103:14 123:9
19	2009	320:18	25	
6:3 134:13 151:13	135:12,22 136:22	202	1:14 6:21 23:7 41:7	3
195	209:7	3:14 6:21	155:3,4 202:6,14	3
176:9	2010	205	202:15 211:19	4:13 20:8,9 33:13
1976	95:6,21,22 96:14	7:3	215:25 217:18	103:10 266:9
69:1 88:7,12	98:8,16 99:7	21	219:25 247:22	3:02
1980s	100:22,25 101:14	6:9 153:20 169:2,3	248:5 249:13,25	211:14,15
191:11	101:17 102:11,13	194:21 212:17	256:11 264:15	3:16
1982	103:2 123:7	220:25 224:9	313:11	211:15,17
295:3	138:21 147:15	232:24,24	253	3:29
1990s	187:21 189:9,14	21,000	212:19 270:2	219:20
162:8,12	190:12 192:10,15	14:21	254	3:31
	192:22 193:6	216	91:25 194:24	219:23
2	194:9,12 195:4	221:8	256	30
2	209:7 216:15	22	92:3,4 170:8	7:16 155:1 202:6
4:11 17:19,20	217:5 314:10,20	6:11 173:10,12,13	25th	247:22 248:5
18:10 77:16,17	315:15	173:14,17 209:24	8:3	249:13 250:1
137:5 139:11	2012	222:4 224:9,14	26	256:12 271:16
187:4 194:23	95:18	226:7,15 232:23	4:21 7:3 205:1,2	272:11 273:16,17
235:4 269:21	2013	232:24,25 289:19	220:1	288:17 298:12
273:25 274:3	179:19,21 180:6	22311	267-0058	300:9 313:11
2.91	276:10	2:4	3:9	302
235:12	2014	224-1133	26th	4:3
2:03	5:7 84:2,23 132:2	2:13	320:18	305
165:10,12	133:3 185:11	227	27	2:12
20	202:20 233:23	7:6	7:6 227:5,6 262:23	307
4:13 6:6 23:4 50:17	234:24,25 235:6,9	227-8008	273	7:19
51:5,8 113:7	235:12,17 236:16	2:18	7:16	31
164:21 165:2,3,18	236:24 239:18	23	2738	7:19 40:18 307:14
217:22 288:3	240:16	6:13 132:8,15	319:2	307:15
300:9	2015/2016	173:9,12 175:17	27705	310
2000	283:9	175:19 226:8	1:18	4:6
189:4 190:14,14	2016	233:5,6 234:2	28	312
191:20 194:12	11:19 12:4 128:5	240:23	7:10 234:10,11	3:19
195:7 204:25	128:23 131:12	2306	280	315
205:4	234:3,13,22	1:17	4:4 55:7 94:5,8	4:3
20004-1454	238:24 240:15	233	29	32
3:14	242:2 243:3 292:1	3:18	7:13 237:14,19	4:15
2000s	2018	234	294	34

90:7	274:25 275:1	6:01	78701	134:20 137:17
3400	463-2400	309:24,25	2:8 3:4	973
2:17	3:14	6:14	7th	2:23 3:9
35	47	309:25	2:8	975
4:17 61:19 90:10	184:24 207:11,18	6:15	<hr/>	3:13
350	478-1236	310:2	8	99
3:8	2:9	6:22	8	213:8
358	48	315:7	4:22 41:15,17,19	995
210:8	207:18	6:23	42:25 77:17	139:10
359	49	315:10	196:20 291:1	
174:1	5:3 307:21	6:25	8,525	
36	4900	317:7,8	6:19	
4:18 236:5,13	2:3	60	816	
37	<hr/>	303:8,9	3:3	
4:21	5	60,000	817	
39	5	199:20	278:7	
166:7	4:17,24 35:11,20	600	820	
391-0197	35:21,24 128:2	2:17,22 284:18	180:15,16	
3:4	135:12,15 203:2	60606	84	
<hr/>	5:14	3:19	5:7	
4	278:3	61	877.370.3377	
4:15 32:21,22	5:15	5:4	1:24	
128:2 203:15	278:6	62	<hr/>	
4:33	5:18	39:25	9	
259:14,15	280:11	624-6300	4:3,24 45:7,8	
4:46	5:20	3:19	9,859	
259:15	280:14	63	6:19	
4:47	5:50	218:7	9:04	
259:17	302:17	631	1:15 8:4	
40	5:51	2:13	90	
23:3 85:18 300:9	302:20	<hr/>	155:6,8,11 262:23	
40,000	50	7	90-some-thousand	
199:20,25 200:7	38:24 39:1,4	4:21 37:10,13,14	218:17	
400	208:10	80:11	90s	
2:12 14:18	51	703	161:22	
404	236:7,13	2:4	91	
2:8	512	713	5:8	
41	2:9 3:4	2:18	917.591.5672	
4:22 38:21	549-7164	73	1:24	
42	2:23	270:22	931-5500	
167:15,20,21	5th	76	2:4	
429	45:13	139:23	94	
213:1	<hr/>	77	46:12 50:10	
45	6	5:6	943	
4:24	4:18 36:17,22	77002	213:2	
463	104:15	2:18	95	

Exhibit 8

Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)

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Abstract

Background: Epidemiologic studies indicate increased ovarian cancer risk among women who use genital powder, but this has not been thoroughly investigated in African American (AA) women, a group with a high prevalence of use. We evaluate the relationship between use of genital powder and nongenital powder in invasive epithelial ovarian cancer (EOC).

Methods: Subjects are 584 cases and 745 controls enrolled in the African American Cancer Epidemiology Study (AACES), an ongoing, population-based case-control study of EOC in AA women in 11 geographic locations in the United States. AA controls were frequency matched to cases on residence and age. Logistic regression was used to calculate ORs and 95% confidence intervals (CI) for associations between genital and nongenital powder exposure and EOC risk, controlling for potential confounders.

Results: Powder use was common (62.8% of cases and 52.9% of controls). Genital powder was associated with an increased risk of EOC (OR = 1.44; 95% CI, 1.11–1.86) and a dose-response relationship was found for duration of use and number of lifetime applications ($P < 0.05$). Nongenital use was also associated with EOC risk, particularly among non-serous EOC cases (OR = 2.28; 95% CI, 1.39–3.74). An association between powder use and upper respiratory conditions suggests an enhanced inflammatory response may explain the association between body powder and EOC.

Conclusions: In a study of AA women, body powder use was significantly associated with EOC risk.

Impact: The results support that body powder is a modifiable risk factor for EOC among AA women. *Cancer Epidemiol Biomarkers Prev*; 25(10); 1411–7. ©2016 AACR.

See related commentary by Trabert, p. 1369

Introduction

Genital powder use may be a modifiable risk factor for epithelial ovarian cancer (EOC), the most deadly of all gynecologic cancers (1). In 2010, the International Agency for

Research on Cancer (IARC) classified perineal (genital) use of nonasbestos-containing, talc-based body powder as "possibly" carcinogenic to humans (2). Although particles of asbestos have been found in older body powder formulations, particularly prior to 1976 (3), more recent body powder formulations no longer contain asbestos (4, 5). However, the relationship between genital powder use and ovarian cancer appears to persist (6). It has been proposed that talc-containing powders may promote cancer development through local inflammation, increased rates of cell division and DNA repair, increased oxidative stress, and increased cytokine levels (7).

A recent pooled analysis of eight population-based case-control studies demonstrated an elevated OR of 1.24 for the association between genital powder use and EOC (6). Some (7–15) but not all (6, 8, 16) previously published studies of talc and ovarian cancer reported a dose-response relationship with genital powder use for frequency, duration, or number of applications. In addition, some studies reported a stronger association among the most common serous histologic subtype (4, 10, 14, 16, 17) although the pooled analysis did not confirm this finding (6). Only one prospective study (17) found a significant association with ever genital talc use and invasive serous EOC (RR = 1.40; 95% CI, 1.02–1.91), although no overall association with EOC was found. The Women's Health Initiative (WHI; ref. 18) did not detect an association with

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Schildkraut et al.

genital talc use and EOC. Neither prospective study found evidence of a dose-response relationship.

Previous studies of genital powder use have included mostly white women. However, two studies reported analyses stratified by race and both found an increased EOC risk among African American (AA) women who used genital talc (14, 15). One study reported a nonsignificant association between one or more years of talc use and risk of ovarian cancer, OR = 1.56, [95% confidence interval (CI), 0.80–3.04] among a small sample of 128 AA EOC cases and 143 AA controls, who were shown to have higher prevalence of talc use compared with whites (14). A second study reported an imprecise but significant association with genital talc use with an OR of 5.08 (95% CI, 1.32–19.6) among a very small sample of 16 cases and 17 controls (15). In this article, we present analyses of the relationship between both genital powder and nongenital powder exposure from the African American Cancer Epidemiology Study (AACES), an ongoing, multicenter case-control study of invasive EOC in AA women.

Materials and Methods

Study population

AACES is an ongoing, population-based, case-control study of invasive EOC in AA women in 11 locations (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Institutional review board approval was obtained from all participating institutions. Methods have been described in detail elsewhere (19). Briefly, cases include AA women 20 to 79 years of age with newly diagnosed EOC. With a goal of enrolling an equal number of cases and controls, controls were AA women identified through random digit dialing, with at least one intact ovary and no history of ovarian cancer, and frequency matched to cases on region of residence and 5-year age categories. Participants complete a baseline telephone interview, which includes detailed questions on demographic characteristics; reproductive, gynecologic, and medical history; hormone therapy (HT) and oral contraceptive (OC) use; cancer family history and lifestyle characteristics including smoking, alcohol consumption, and physical activity. In an effort to obtain information from as many women as possible, a short version of the questionnaire is offered to those who would otherwise refuse to participate in the study. Accrual began in December 2010 and as of August 31, 2015, 593 cases and 750 controls were enrolled. Eligibility for this analysis was restricted to participants for whom data on body powder use and all covariates were available, resulting in a final sample size of 584 cases and 745 controls; of these, 49 cases and 16 controls completed the short questionnaire.

Exposure to body powder and talc

In the baseline interview, participants were asked whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered "regular users" if they reported using any of these powders at least one time per month for at least 6 months, and "never users" if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas. Participants were categorized according to their type of

application as nongenital use only, genital use only, or genital and nongenital use. Lifetime number of applications was calculated by multiplying the number of body powder applications per month by the number of months used. Occupational exposure to talc (yes, no) was available only for subjects completing the long baseline survey.

Statistical analysis

The prevalence of demographic characteristics was calculated and *t* tests and χ^2 tests were performed to compare distributions between cases and controls. Because of the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), we merged this exposure category with those who reported use of both nongenital and genital powder, creating an exposure category of "any" genital powder use. Unconditional multivariable logistic regression was performed to calculate ORs and 95% CIs for the associations between body powder exposure ("only" nongenital use, and "any" genital use) and risk of EOC. Body powder exposure was further examined by frequency of use (less than 30 times per month, daily), duration of use categorized as less than the median or the median and greater among the controls (<20 years, ≥ 20 years), and lifetime number of applications categorized as less than the median or the median and greater among controls (<3,600, $\geq 3,600$ lifetime applications). Trend tests for frequency, duration, and lifetime applications of powder use by route of exposure were conducted separately in two subsamples: only nongenital users plus never users and any genital users plus never users. For each subsample, each of the above variables was entered into a logistic regression as multiple indicator variables representing three levels and two degrees of freedom (i.e., for frequency of use: no exposure, less than daily, daily), adjusting for confounders. Trends were evaluated by statistical tests for the association between frequency/duration/lifetime applications with EOC risk, using Wald tests to simultaneously test the equality of parameter estimates with zero. Because experimental data suggest a relationship between inhaled inert particles and asthma (20), a logistic regression analysis was conducted to determine the association between body powder use and upper respiratory conditions (yes/no), controlling for EOC case/control status.

Covariates included reference age in years (age at diagnosis for cases and age at baseline interview for controls); study site [Alabama, Louisiana, New Jersey, North Carolina, Ohio, South Carolina, Texas, Michigan and Illinois (combined because of sample size and regional similarities), Georgia and Tennessee (combined because of sample size)]; education (\leq high school, some after high school training, college or graduate degree); parity (0, 1, 2, 3+); duration of oral contraceptives (never, <60 months, ≥ 60 months); history of tubal ligation (yes/no); family history of breast or ovarian cancer in a first-degree relative (yes/no); smoking (ever/never); and body mass index (BMI < 25, 25–29.9, ≥ 30 kg/m²). Two class action lawsuits were filed in 2014 (21) concerning possible carcinogenic effects of body powder, which may have influenced recall of use. Therefore, year of interview 2014 or later (yes/no) was included as a covariate in the logistic regression models. To assess potential reporting bias, we also examined whether there were differences in prevalence of reported powder use by interview year (before 2014, 2014 and later) for cases and controls as well as whether interview year was an effect modifier of the relationship between powder use and EOC risk.

Analyses by the histologic subtype versus all controls were also conducted and heterogeneity of risk estimates was tested by seemingly unrelated regression (22). Because of the missing data for histology, 48 cases were omitted from these analyses. Through stratified analyses, we also assessed possible effect modification of the association with powder use and ever use of HT among postmenopausal women using logistic regression. Experimental data show that the inflammatory response is enhanced in the presence of estrogen and progesterone and we therefore tested for interaction of the association with body powder use by menopausal status (20). Logistic regression and trend analyses were performed using SAS version 9.4 (SAS Institute).

Results

Descriptive statistics for cases and controls are presented in Table 1. Cases were older than controls and had lower educational achievement. Although this study was designed to match controls to cases by 5-year age group, the difference in the age at diagnosis/age at interview may, in part, be because the study is actively enrolling subjects. However, age ranges of cases (20–79 years) and controls (20–79 years) overlap. Significant differences in the distributions of well-established risk factors, including a shorter duration of oral contraceptive use, and lower prevalence of tubal ligation in cases as compared with controls, were as expected. As expected, parity was lower among cases compared with controls, but the difference was not significant. In addition, cases were more likely to report a family history of breast or ovarian cancer. No significant difference in the median years of use of body powder or occupational exposure of talc in cases compared with controls was observed.

Table 2 shows the results of logistic regression models examining the relationship between any use of body powder (either "only" nongenital powder or "any" genital powder) as well as the use of body powder by type of application: "only" nongenital powder use or "any" genital powder use. Adjusting for potential confounders, we observed a significant positive association between any powder use and EOC (OR = 1.39; 95% CI, 1.10–1.76). The OR for the association with "any" genital powder use was 1.44 (95% CI, 1.11–1.86). An OR of 1.31 (95% CI, 0.95–1.79) for the measure of association between "only" nongenital powder use and EOC was only slightly lower in magnitude compared with the association when "any" genital use was reported, but not statistically different from one another ($P = 0.56$). In 2014 and later, we observed an increase in any powder use of 12% and 6% of cases and controls, respectively. Although increased, these exposure prevalences were not significantly different from those interviewed before 2014 ($P = 0.30$). For those interviewed in 2014 or later, we observed an OR for "any" genital powder use of 2.91 (95% CI, 1.70–4.97) compared with 1.19 (95% CI, 0.87–1.63) before 2014. We observed a weaker OR of 1.26 (95% CI, 0.69–2.32) for 2014 and later compared with 1.40 (95% CI, 0.96–2.03) before 2014 for those who reported "only" nongenital use. A test for effect modification by year of interview was statistically significant ($P = 0.005$).

The ORs for the association between daily use of powder for either "only" nongenital powder use (OR = 1.53; 95% CI, 1.00–2.35) or "any" genital powder use (OR = 1.71; 95% CI, 1.26–2.33) with EOC were larger in magnitude than ORs for less than daily use compared with never use but the test for trend was significant for only "any" genital powder use (Table 2). There is a

Table 1. Characteristics of ovarian cancer cases and controls in the African American Cancer Epidemiology Study (AACES)

	Cases (<i>n</i> = 584) <i>n</i> (%)	Controls (<i>n</i> = 745) <i>n</i> (%)	<i>P</i>
Age (years)			<0.01
<40	31 (5.3)	80 (10.7)	
40–59	299 (51.2)	398 (53.4)	
60+	254 (43.5)	267 (35.8)	
Range (years)	20–79	20–79	
Education			0.02
High school or less	262 (44.9)	278 (37.3)	
Some after high school training	145 (24.8)	210 (28.2)	
College or graduate degree	177 (30.3)	257 (34.5)	
Body mass index (kg/m ²)			0.09
<24.9 (under- and normal weight)	86 (14.7)	140 (18.8)	
25–29.9 (overweight)	148 (25.3)	197 (26.4)	
>30 (obese)	350 (59.9)	408 (54.8)	
Parity (# of live births)			0.06
0	105 (18.0)	96 (12.9)	
1	113 (19.4)	141 (18.9)	
2	136 (23.3)	198 (26.6)	
3+	230 (39.4)	311 (41.6)	
Tubal ligation			0.02
Yes	201 (34.4)	302 (40.5)	
No	383 (65.6)	443 (59.5)	
Oral contraceptive use			<0.01
Never	180 (30.8)	155 (20.8)	
<60 months	230 (39.4)	334 (44.8)	
>60 months	174 (29.8)	256 (34.4)	
First-degree family history of breast or ovarian cancer			<0.01
Yes	149 (25.5)	132 (17.7)	
No	435 (74.5)	613 (82.3)	
Menopausal status			0.31
Premenopausal	158 (27.2)	221 (29.7)	
Postmenopausal	423 (72.8)	522 (70.3)	
Hormone therapy			0.10
Ever use	118 (20.3)	125 (16.8)	
Never use	463 (79.7)	618 (83.2)	
Smoking			0.48
Ever	257 (44.0)	313 (42.0)	
Never	327 (56.0)	432 (58.0)	
Hysterectomy ^a			0.43
Yes	141 (24.1)	166 (22.3)	
No	443 (75.9)	579 (77.7)	
Body powder use (median years) ^b	20	20	0.48
Occupational talc exposure ^c			0.16
Yes	58 (10.8)	62 (8.5)	
No	477 (89.2)	667 (91.5)	
Histologic subtype ^d			
Serous	393 (73.2)		
Mucinous	24 (4.5)		
Endometrioid	72 (13.4)		
Clear cell	13 (2.4)		
Other	35 (6.5)		

^aDefined as hysterectomy 2 years prior to diagnosis for cases and 2 years prior to interview for controls.

^bAmong body powder ever users only.

^cData not available for participants who completed the short questionnaire (49 cases and 16 controls).

^dData missing on histologic subtype for 47 cases.

moderately stronger association for ≥ 20 years of "any" genital powder use (OR = 1.51; 95% CI, 1.11–2.06) compared with <20 years of use (OR = 1.33; 95% CI, 0.95–1.86; $P_{\text{trend}} = 0.02$). No dose–response with years of use was detected for "only" nongenital powder use. The ORs for the number of lifetime applications

Schildkraut et al.

Table 2. Adjusted ORs for the associations between mode, frequency, and duration of body powder use and ovarian cancer in the AACES

Exposure	Cases (n = 584) n (%)	Controls (n = 745) n (%)	OR ^a (95% CI)
Body powder use			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Ever use	367 (62.8)	394 (52.9)	1.39 (1.10–1.76)
Body powder use by location			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Only nongenital use	119 (20.4)	140 (18.8)	1.31 (0.95–1.79)
Any genital use	248 (42.5)	254 (34.1)	1.44 (1.11–1.86)
Interview date <2014 (n = 351)		(n = 571)	
Never use	147 (41.9)	286 (48.4)	1.00 (Referent)
Only nongenital use	76 (21.7)	104 (17.6)	1.40 (0.96–2.03)
Any genital use	128 (36.5)	201 (34.0)	1.19 (0.87–1.63)
Interview date >2014 (n = 233)		(n = 154)	
Never use	70 (30.0)	65 (42.2)	1.00 (Referent)
Only nongenital use	43 (18.4)	36 (23.3)	1.26 (0.69–2.32)
Any genital use	120 (51.5)	53 (34.4)	2.91 (1.70–4.97)
Frequency of use			
Never use	217 (37.3)	351 (47.2)	1.00 (Referent)
Only nongenital use			
Less than daily	61 (10.5)	82 (11.0)	1.15 (0.78–1.71)
Daily	58 (10.0)	58 (7.8)	1.53 (1.00–2.35)
<i>P</i> _{trend}			0.09
Any genital use			
Less than daily	88 (15.1)	119 (16.0)	1.12 (0.80–1.58)
Daily	158 (27.2)	134 (18.0)	1.71 (1.26–2.33)
<i>P</i> _{trend}			<0.01
Duration of use			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
<20 years	59 (10.2)	68 (9.2)	1.37 (0.91–2.07)
>20 years	60 (10.3)	70 (9.5)	1.28 (0.85–1.93)
<i>P</i> _{trend}			0.13
Any genital use			
<20 years	101 (17.4)	118 (15.9)	1.33 (0.95–1.86)
>20 years	144 (24.8)	134 (18.1)	1.52 (1.11–2.07)
<i>P</i> _{trend}			0.02
Lifetime body powder applications			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
Below median (<3,600 applications)	60 (10.3)	72 (9.7)	1.35 (0.90–2.03)
Above median (>3,600 applications)	59 (10.2)	66 (8.9)	1.30 (0.86–1.97)
<i>P</i> _{trend}			0.14
Any genital use			
Below median (<3,600 applications)	92 (15.9)	119 (16.1)	1.16 (0.83–1.63)
Above median (>3,600 applications)	152 (26.2)	133 (17.9)	1.67 (1.23–2.26)
<i>P</i> _{trend}			<0.01

^aAdjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

of body powder at or above and below the median support a dose–response with "any" genital powder use ($P_{\text{trend}} < 0.01$) but not for nongenital powder use ($P_{\text{trend}} = 0.14$).

A report of any occupational talc exposure, for those completing the long baseline questionnaire, was found to be positively, but not statistically significantly, associated with EOC (OR = 1.31; 95% CI, 0.88–1.93; data not shown). Table 3 shows an OR of 1.38 (95% CI, 1.03–1.85) for the association in serous cases with "any" genital powder use. Among serous cases, the OR for "only" nongenital powder use was lower in

magnitude and not significant (OR = 1.10; 95% CI, 0.76–1.58). Compared with serous cases, larger and statistically significant ORs are found for the associations with type of powder application in nonserous EOC cases; ORs were 1.63 (95% CI, 1.04–2.55) and 2.28 (95% CI, 1.39–3.74), for "any" genital powder use and "only" nongenital powder use, respectively (Table 3). A comparison of adjusted odds ratios between serous and nonserous histologic subtypes and powder use, detected a difference in "only" nongenital powder use ($P = 0.008$), but did not detect significant differences in association for "any" genital powder use ($P = 0.50$).

The stratified results by menopausal status (Table 4) suggest differences in the association for exposure to "only" nongenital powder use among premenopausal where no association is seen for "only" nongenital powder use, whereas the association with the risk of EOC and "any" genital use is elevated. Among postmenopausal women, we observed positive associations of similar magnitude for both the association between EOC and "only" nongenital powder use (OR = 1.49; 95% CI, 1.04–2.15) and "any" genital powder use (OR = 1.41; CI, 1.03–1.92). However, tests of interaction indicate no evidence for interaction by menopausal status for either route of exposure. Among menopausal women, analyses stratified by HT use suggest a stronger association among users compared with nonusers of HT for both routes of applications, although we detected a borderline, nonsignificant interaction for the associations with "any" genital body powder by HT use ($P = 0.06$). The test for interaction for nongenital body powder by HT use was not significant ($P = 0.76$).

To further consider the underlying mechanism for the relationship between use of body powder and the risk of EOC, we calculated the association between both "only" nongenital powder use and "any" genital powder use and having an upper respiratory condition. Controlling for case–control status, age at diagnosis/interview, study site, education, smoking, and BMI, we found ORs of 1.35 (95% CI, 0.89–2.05) and 1.45 (95% CI, 1.03–2.05) for "only" nongenital and "any" genital powder use, respectively, in relation to a reported respiratory condition, respectively (data not shown). A nonsignificant, but elevated OR of 1.26 (95% CI, 0.77–2.06) was observed with occupational exposure to talc and respiratory conditions (data not shown).

Table 3. Adjusted ORs for the associations between talc use and serous/nonserous EOC

Histologic subtype ^a	Cases n (%)	Controls n (%)	OR ^b (95% CI)
Serous (n = 392)			
Never use	156 (39.8)	351 (47.1)	1.00 (Referent)
Only nongenital use	71 (18.1)	140 (18.8)	1.10 (0.76–1.58)
Any genital use	165 (42.1)	254 (34.1)	1.38 (1.03–1.85)
Nonserous (n = 144)			
Never use	44 (30.6)	351 (47.1)	1.00 (Referent)
Only nongenital use	42 (29.2)	140 (18.8)	2.28 (1.39–3.74)
Any genital use	58 (40.3)	254 (34.1)	1.63 (1.04–2.55)

^aTest for interaction for association with powder use by serous and nonserous histologic subtype and route of body powder exposure was $P = 0.008$ for "only" nongenital powder use and $P = 0.50$ for "any" genital powder use.

^bAdjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

Table 4. Adjusted ORs for the association between EOC risk and body powder by menopausal status and HT use

Exposure	Premenopause			Postmenopause		
	Cases (n = 158) n (%)	Controls (n = 221) n (%)	OR ^a (95% CI)	Cases (n = 423) n (%)	Controls (n = 522) n (%)	OR ^a (95% CI)
Body powder use ^b						
Never use	59 (37.3)	103 (46.6)	1.00 (Referent)	157 (37.1)	247 (47.3)	1.00 (Referent)
Only nongenital use	22 (13.9)	42 (19.0)	0.90 (0.44–1.84)	97 (22.9)	98 (18.8)	1.49 (1.04–2.15)
Any genital use	77 (48.7)	76 (48.7)	1.50 (0.87–2.57)	169 (40.0)	177 (33.9)	1.41 (1.03–1.92)
HT ever/never use ^{c,d,e}						
HT ever use						
Never use				34 (32.1)	55 (48.7)	1.00 (Referent)
Only nongenital use				23 (21.7)	23 (20.4)	1.74 (0.77–3.92)
Any genital use				49 (46.2)	35 (31.0)	2.68 (1.33–5.40)
HT never use						
Never use				122 (38.9)	191 (46.9)	1.00 (Referent)
Only nongenital use				73 (23.3)	75 (18.4)	1.51 (0.99–2.29)
Any genital use				119 (37.9)	141 (34.6)	1.24 (0.87–1.79)

^aAdjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

^bTest for interaction between menopausal status and route of body powder exposure was nonsignificant for only non-genital use ($P = 0.21$) and any genital use ($P = 0.85$) compared with never use.

^cRestricted to postmenopausal women.

^dTest for interaction between HT use and only nongenital use was nonsignificant ($P = 0.76$).

^eTest for interaction between HT use and any genital use was nonsignificant ($P = 0.06$).

Discussion

In the largest EOC case-control study in AA women to date, we observed a positive association between regular use of powder and EOC regardless of the route of application. Users of genital powder were shown to have greater than a 40% increased risk of EOC compared with an increased risk of more than 30% among those who used only nongenital powder. The OR for the association with genital powder use in the current study is consistent with the association reported in AA women by Wu and colleagues (14). Of note, a high proportion of EOC cases (63%) and controls (53%) reported any use of body powder. A dose-response trend was evident for median years of use or greater as well as median number or greater of lifetime applications of "any" genital powder but not for use of "only" nongenital powder. Our results support that the association with "any" genital powder use is similar in premenopausal and postmenopausal women, whereas there appears to be an association with use of "only" nongenital powder use among postmenopausal but not premenopausal women. Associations were found among nonserous EOC cases and among postmenopausal users of HT exposed to either genital or nongenital powder.

Most previous case-control studies have not found an association between nongenital powder use and ovarian cancer, including a large pooled analysis by Terry and colleagues who reported an adjusted OR of 0.98 (95% CI, 0.89–1.07; refs. 6, 16). No prospective studies have evaluated nongenital powder use, nor has any study examined these associations by histologic subtype (17, 18). In the current study, the overall association with nongenital use and EOC was similar to that for genital powder use though it did not reach statistical significance possibly due to small numbers and random variation. However, we also did not find a dose-response relationship with frequency, duration, or lifetime applications of "only" nongenital powder use. Furthermore, we did not detect a significant association with use of "only" nongenital powder among serous cases, whereas the OR for the association with use of "only" nongenital powder showed over a 2-fold signif-

icant increased risk for nonserous EOC. In fact, we found a statistically significant difference between associations by subtype for "only" nongenital use. Given the inconsistency with previous published findings, it is also reasonable that under-reporting genital powder use, such as abdominal powder use that reaches the genital area, may have led to a spurious result. Another possible explanation for our finding may be that there is a higher inflammatory response in AAs compared with whites (23–25). Our results also suggest that the route of powder exposure may have different effects by histologic subtype. As most high-grade serous EOC, but not nonserous subtypes, arise in the fallopian tubes (26), it is possible that direct exposure through the genital tract specifically affects this disease subtype. The association with any genital powder use and nonserous cases may be due to the overlap between genital and nongenital powder use (83% of cases and 83% of controls). We were unable to examine associations with "only" genital powder users due to sample size considerations. In contrast, nongenital powder use may be related to inhalation of the exposure through the lungs. Several large pooled analyses have demonstrated risk factor associations with inflammatory-associated exposures, such as smoking (27), endometriosis (28), and obesity (29) with nonserous histologic subtypes of ovarian cancer but not high-grade serous EOC, providing a plausible theoretical basis for differences we found in associations by histologic subtype.

Akin to talc powders, titanium dioxide (TiO₂) is another inert particle that induces an inflammatory response upon inhalation and has been considered to be "possibly carcinogenic to humans" by IARC (2). Experimental evidence of enhanced inflammation due to exposure to inert environmental particulates of TiO₂ showed inhibition of phagocytic activity of alveolar macrophages in pregnancy, and was found to be associated with increased asthma risk in the offspring of BALB/c mice exposed to TiO₂. In this study, elevated estrogen levels during pregnancy were found to contribute to the resulting asthma risk (20). Our findings also support that enhanced airway inflammation is due to exposure to inert particles.

Schildkraut et al.

Consistent with a recent study (15) where an association with powder use and asthma was reported, the relationship between body powder use and respiratory conditions likely reflects an enhanced inflammatory response due to powder use, suggesting a mechanism by which EOC risk is increased. Therefore, lung inhalation of powder could be a biologically plausible mechanism for the association between nongenital body powder use and increased EOC risk, particularly in nonserous EOC cases.

To further explore whether estrogen influences the inflammatory response, we performed stratified analyses by menopausal status. We did not see a difference in the association with premenopausal compared with postmenopausal use of "any" genital powder use, which is not consistent with a recent report (15) where an association with premenopausal use but not postmenopausal use was found. However, consistent with this report, we found a stronger association between "any" genital powder use and EOC among postmenopausal women who reported HT use compared with nonusers. This finding is also consistent with experimental data showing that in the presence of estrogen and/or estrogen and progesterone, the ability of macrophages to clear inert particulates is altered, enhancing the inflammatory response leading to the development of asthma in mouse offspring (20). It has also been proposed that chronic inflammation, resulting from exposure to body powder, whether through inhalation or through a transvaginal route, may exert a suppressive effect on adaptive immunity, leading to increased risk of EOC (30). These findings suggest that AA women may be particularly susceptible to exposure to body powder due to having higher endogenous estrogen levels compared with white women (31, 32). Because of the limited sample size, we were not able to evaluate associations with the timing or duration of HT use or the concurrent effects of both HT and powder use. Tests for interaction of the associations in the stratified analyses by HT use were not significant and our findings should be considered exploratory.

The results of the current study showed that genital powder use was associated with ovarian cancer risk in AA women and are consistent with localized chronic inflammation in the ovary due to particulates that travel through a direct transvaginal route. The dose-response observed for duration of genital powder use provides further evidence for the relationship between genital powder and overall EOC risk. Our data suggest that the increased risk due to use of genital powder applies to both serous and nonserous histologic subtypes of EOC. Use of "only" nongenital powder was not found to be associated with the serous subtype, but our data suggest a relationship with nonserous EOC. The association with serous EOC is consistent with several previous studies (4, 6, 14–17). Only the pooled analysis found associations with the endometrioid and clear cell subtypes (6). The association with any occupational talc exposure and EOC (OR = 1.31; data not shown), though not statistically significant, is also consistent with the results for "only" nongenital powder use and suggest other routes of exposure, aside transvaginal, may effect EOC risk.

A recent publication of data from the WHI, which did not find an association with genital talc use and ovarian cancer (18), was accompanied by an editorial that emphasized the challenges in assessing the exposure to talc due to the reliance on self-report (33). This limitation in the measurement of the exposure variables in the current study needs to be considered when interpreting our results. The possibility of differential misclassification exists in a

case-control study such as AACES, especially due to heightened awareness of the exposure as a result of two recent class action lawsuits (21). Because of such publicity, we adjusted for date of interview in the analysis. However, there is still a possibility that recall bias may have caused some inflation of the ORs. Although our findings suggest that the publicity of the class action lawsuits may have resulted in increased reporting of body powder use, our data do not support that recall bias alone before 2014 versus 2014 or later would account for the associations with body powder use and EOC. It is possible that the lawsuits sharpened memories of body powder use and improved the accuracy of reported use for both cases and controls interviewed in 2014 or later. As the association with nongenital body powder use is not consistent with the published literature, the possibility of misclassification of exposure, residual confounding, or a chance finding cannot be ruled out as an explanation for the associations with nongenital powder use.

In summary, we found that the application of genital powder is associated with serous and nonserous EOC in AA women, a novel observation in this population that is consistent with some large studies in whites. Our data are consistent with the notion that localized chronic inflammation in the ovary caused by exposure to genital powder contributes to the development of EOC. Although associations with nongenital powder use and EOC have not been previously reported, we cannot rule out the possibility that this relationship may be specific to AA women. The high prevalence of exposure to both genital and nongenital body powder among AA women compared with the mostly white subjects (41%), as in the large pooled analysis (6), underscores the importance of the study's findings. The results of the current study suggest that the use of body powder is an especially important modifiable risk factor for EOC in AA women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Cancer Epidemiology, Biomarkers & Prevention

Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)

Joellen M. Schildkraut, Sarah E. Abbott, Anthony J. Alberg, et al.

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Exhibit 9

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
REBECCA SMITH-BINDMAN, MD**

Date: November 15, 2018



Rebecca Smith-Bindman, MD

The Relationship Between Exposure to Perineal Talc Powder Products and Ovarian Cancer

Expert Report

Rebecca Smith-Bindman, MD

Professor, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics,
Gynecology and Reproductive Science and Director, Radiology Outcomes Research Lab
University of California San Francisco

Table of Contents

<i>I. Executive Summary.....</i>	<i>4</i>
<i>II. Expertise of Dr. Smith-Bindman.....</i>	<i>6</i>
Education and Employment	6
Research Expertise.....	6
Knowledge of Relevant Study Designs	6
Experience as a Medical Expert.....	8
<i>III. Background: Ovarian cancer and Talc as a Modifiable Risk Factor.....</i>	<i>8</i>
Ovarian Cancer	8
Histologic types	9
Risk Factors	11
Etiology: Origins, Causes, Development and Inflammation	12
Association of Ovarian Cancer with Talc Powder Products	13
Why Talc Powder Products were Initially Suspected as Causing Ovarian Cancer.....	13
Asbestos	14
Talc.....	15
Heavy Metals.....	16
<i>IV. Overview of Publications on Genital use of Talc powder products and Ovarian Cancer.....</i>	<i>16</i>
Explanation of study designs and article types	16
Table of Reviewed Publications	18
Quantifying Exposures	19
Summary of Data	19
Cohort Studies	19
Systematic Reviews	22
Pooled Data	27
Case-Control Trials.....	29
<i>V. Rationale for and Explanation of the New Systematic Review.....</i>	<i>30</i>
<i>VI. New Systematic Review of Literature Quantifying Association Between Regular Frequent Genital (Perineal) Talc powder products Application and Ovarian Epithelial Cancer Risk with A Focus On Invasive Serous Cancer.....</i>	<i>31</i>
Literature Search	31
Article Selection.....	31
Exclusion	32
Defining Talc powder products Use.....	32

Stratification of Analyses: Focus on a Single Histologic Type Where Possible	32
Type of Exposures.....	32
Statistical Analysis	33
Results.....	33
New Systematic Meta analytic review: Summary.....	34
Overall Summary of the Epidemiology Data Describing the Association Between Talc Powder Products and Ovarian cancer	34
<i>VII. Other Relevant Factors</i>	<i>35</i>
Research Supporting Talc Association with Ovarian Cancer: Transit to ovary and Risk Reduction on Interruption.....	35
Interactions	32
Risks Over Time	32
Variation in Risk when Talc Use is Discontinued.....	35
<i>VIII. Consideration of Causality of Talc powder products and Ovarian Cancer : Bradford Hill Factors</i>	<i>35</i>
A) Strength of Association.....	36
B) Consistency of Associations in Different Populations and Studies	38
C) Specificity Between Cause and Outcome	39
D) Temporality.....	39
E) Dose Response.....	39
F) Biologic Plausibility: Factors Linking Talc and Ovarian Cancer	40
G) Coherence and Consistency with Understood Biology.....	41
H) Experimental Evidence	41
I) Analogy	41
<i>References</i>	<i>42</i>

I. Executive Summary

Substantial evidence supports a strong positive association between ovarian cancer and genital exposure to talcum powder products and that regular exposure to talcum powder products causes ovarian cancer in some women. Talc is a naturally occurring mineral used in cosmetic products because of its desirable chemical properties such as being soft and absorbent. Women who have had regular exposure of the genitals (specifically the perineal region from the pubic area to the anal area) to talcum powder products are at increased risk of developing invasive ovarian cancer, in particular serous cancer, the most common and most lethal form. In the United States, a substantial portion of women report having ever used talc powder products at some point in their life. The most commonly reported frequency of talcum powder product use is daily. Women who use talcum powder products daily increase their risk of developing ovarian cancer significantly. Regular exposure causes ovarian cancer in some women.

I was asked to review the medical and scientific literature regarding the relationship between genital talcum powder product use and ovarian cancer and determine whether the relationship is causal. For this extensive analysis and report, I applied the same methodology with the same scientific rigor that I use in my research and clinical practice. I reviewed 43 relevant publications presenting scientific data on the association between ovarian cancer and exposure to talc powder products: 4 cohort studies, 8 systematic reviews, 2 studies that pooled data from multiple individual studies, and 30 case-control studies. I also read numerous review articles, and systematic reviews on related topics such as those completed by the International Agency on Research on Cancer (IARC). I also completed my own, new systematic review on of the studies that I reviewed as part of this report. This report contains my overview of these publications plus a detailed new systematic review of the studies that I conducted. After reading, evaluating, and summarizing these publications, in my expert opinion, I do not have any uncertainty that regular exposure to talc powder products increases a woman's chance of developing epithelial ovarian cancer. In my expert opinion, regular exposure to talcum powder products causes ovarian cancer

Quantifying the precise magnitude of the association is more difficult than establishing the association. The association will certainly vary by demographic and reproductive factors and whether women have other underlying ovarian cancer risk factors and exposures. With that caveat, **it is my opinion that women exposed to perineal talc powder products on a regular basis have about a 50% increase in their subsequent risk of developing invasive serous ovarian cancer**, compared to women who do not regularly use talc and even after accounting for other ovarian cancer risk factors. This estimate is supported by existing publications and my quantitative review of the scientific literature that focused on summarizing studies that addressed regular exposure to talc powder products as a risk factor for epithelial ovarian cancer, and in particular serous cancer. Talcum powder exposure is associated with other epithelial cancer subtypes (in particular, clear cell and endometrioid carcinoma), but because these cancers are less common, and because fewer studies have evaluated these cancers in sufficient numbers, quantifying the associations is more difficult. While some publications estimated talc powder products have a slightly greater risk of these cancer subtypes, others

estimated a slightly lower risk of these cancer subtypes. In my opinion, this risk is likely overall in about the same range as for serous cancer, but I would estimate slightly less at 40% increased risk.

The epidemiological evidence documents a strong, positive association between exposure to talcum powder products and ovarian cancer and that regular exposure causes ovarian cancer. The epidemiological evidence alone does not confirm the mechanism by which talc powder product increases ovarian cancer risk, nor does it confirm the specific component in talcum powder products that makes it carcinogenic. Nonetheless, the literature provides compelling evidence that exposure to talcum powder products leads to chronic inflammation and that the inflammation induces a strong biological response that results in the induction, promotion, and growth of cancer. Further, there is evidence that several highly carcinogenic agents are components of the talcum powder products. These include, most importantly, asbestos, a Group 1 carcinogen that the International Agency for Research on Cancer (IARC) has determined causes ovarian cancer. I have seen evidence that talcum powder products contain asbestos. Second, talcum powder products contain asbestiform talc particles which have a similarity in structure to asbestos fibers (and which IARC concludes are carcinogenic). Lastly, talcum powder products contain numerous heavy metals such as, nickel, chromium, (Group 1 carcinogens) and cobalt (Group 2 carcinogen) according to IARC. These components are carcinogenic (cause cancer) and can contribute to the carcinogenicity of talcum powder products. Observational and experimental data confirm that talcum powder product particles applied to the perineum can reach the fallopian tubes and ovaries through the vagina, supporting that talc particles applied to the perineum can deposit on the ovaries. Surgery that impedes the movement of particles from the perineum to the ovaries such as hysterectomy (uterine removal) or tubal ligation (tying or blocking the fallopian tubes to the ovaries), reduces the elevated risk of ovarian cancer from exposure to talcum powder products. This finding supports that local tissue response and inflammation in the fallopian tubes and/or ovaries from talcum powder products (with components) causes the elevated ovarian cancer risk.

In summary, **from my review of the scientific literature and my own analysis, it is my opinion that genital exposure to talcum powder products is an actionable and causative risk factor for ovarian cancer.** As a physician involved in women's health issues, I view talcum powder usage as a modifiable "lifestyle" risk factor that should be avoided because of the substantial risk to health and lack of therapeutic benefit. An elevated risk of 50% is significant and results in a large number of unnecessary ovarian cancers given the large number of women exposed. Depending on estimates of how many women regularly use talcum powder products, between 7% and 20% of all ovarian cancers and 14% - 39% of invasive serous cancers (the most aggressive and feared cancer type) are caused by the use of talcum powder products. These cancers can be prevented if women do not use talcum powder products.

II. Qualifications

Education and Employment

I am a professor of Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Medicine, and Health Policy at the University of California San Francisco (UCSF) School of Medicine. I graduated from Princeton University with a degree in structural engineering (with combined majors in engineering and architecture) and attended UCSF medical school. My training after medical school included an internship, radiology residency, and clinical fellowship in women's health and a research fellowship in epidemiology and biostatistics in the UCSF Departments of Medicine and Epidemiology and Biostatistics.

I am a clinician-scientist. My clinical work includes one day a week in the Department of Radiology and Biomedical Imaging, with a focus on women's health imaging. I work in the ultrasound section, where a large proportion of the work is focused on the diagnosis of ovarian abnormalities (cancer and other functional issues). I run the UCSF Radiology Outcomes Research Lab, spending most of my time on clinical research and leading large epidemiological studies. I teach in the UCSF School of Medicine and Department of Epidemiology and Biostatistics.

Research Expertise

My research expertise is in epidemiology, outcomes research, comparative effectiveness, health services research, and dissemination and implementation sciences. My epidemiological studies have evaluated the quality, use, accuracy, predictive value, and impact of diagnostic testing on patient health. I have measured the risks and benefits of medical imaging in different contexts and different populations. Much of the research is in women's health, including diagnoses of cancers such as ovarian, endometrial, thyroid and breast. I have led many large, multi-institutional research projects. These projects are typically collaborative, involving researchers and clinicians with diverse expertise including radiology, obstetrics and gynecology, medicine, biostatistics, epidemiology, economics, demography, social sciences, medical informatics, radiation science, and dissemination and implementation science.

I have been a prolific researcher. I have led projects funded by more than 50 million dollars in research grants—entirely focused on cancer diagnosis and prediction. The research has been published in the most prestigious medical journals including the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Journal of the American Medical Association*, *Journal of the American Medical Association Internal Medicine*, *Journal of the National Cancer Institute*, *Obstetrics and Gynecology*, and leading radiology specialty journals such as *Radiology* and *Journal of the American College of Radiology*.

Knowledge of Relevant Study Designs

Several of my published studies have been systematic, meta-analytic, quantitative reviews of the published literature. Meta-analyses review existing evidence on a topic and summarize

and re-analyze data from earlier studies. My systematic reviews focused on the diagnoses of endometrial cancer, breast cancer, and a range of birth defects including trisomy 21 (Down syndrome) and trisomy 18 (Edwards Syndrome). Many of my reviews were published in prestigious medical journals, reflecting their scientific rigor based on an in-depth understanding of how to combine and review results from different studies in a scientifically valid and reproducible way.

Several of my recent research projects quantified the variation in radiation dose associated with medical imaging and the expected impact of this variation on cancer outcomes. This work has brought attention to the need for better standards in medical imaging. I am currently leading two large, multi-institutional epidemiological projects on medical radiation funded by the National Institutes of Health. One project is collecting radiation dose measures associated with computed tomography (CT) imaging from more than 150 hospitals in the United States, Europe, and Asia and testing the impact of providing feedback and education to radiologists on average and high doses. The second project is a multinational epidemiological study on childhood cancer. This project is assessing the risk of cancer associated with medical imaging among 1 million children and 1 million pregnant patients after accounting for a range of other cancer risk factors. The study will be the first to quantify the risk of medical imaging including CT among a large group of patients and uses novel methods to accurately estimate radiation dose from imaging.

I have expertise in a range of research study designs. The projects I currently lead (each funded by the National Institutes of Health or the Patient-Centered Outcomes Research Institute for between 9 - 15 million dollars each) have designs selected to be appropriate for the research question. For example, the study assessing the risk of cancer from medical imaging uses a *case-control study design, in which data are collected on a group of patients and those with a condition (cases), are matched to similar patients without the condition (controls)*. Matching people with a disease to people of similar age, gender, and other factors who do not have the disease allows researchers to determine if circumstances such as exposure to a potential toxin influence disease development.

My project on medical imaging uses a *cohort design, comparing groups of people (cohorts) in a population, some exposed to a potential disease agent and some not exposed*, to see if the agent influences disease. My study on radiation doses from CT uses a *randomized controlled design, in which individual patients are randomly assigned to different treatments* so their effectiveness can be compared. I am studying lung nodules using a *cluster-randomized controlled trial design that randomly assigns groups of people in similar circumstances (for example because they all see the same doctor) to different treatments* so the effects of the treatments can be compared.

I have a deep understanding of how epidemiological studies are conducted. I understand what study designs are suitable to particular datasets, populations, and research questions and the advantages and disadvantages of each design. This is relevant as no single study

design is “best;” there are strengths and weaknesses of each. The most appropriate and valid study design varies based on the research question being asked.

Experience as a Medical Expert

For the National Academy of Medicine, I have contributed to several reports, including Saving Women’s Lives (2004), Improving Mammographic Quality Standards (2005), and Breast and the Environment: A Life Course Approach (2012), for which I wrote a review on the association between radiation exposure and breast cancer (Appendix). In addition to this research, I am actively involved in raising awareness of the need for better standards and greater safety around medical imaging, in particular related to radiation exposure. I have spoken at the US Food and Drug Administration, testified before the US Congress on several occasions, and worked with leading professional societies to focus attention on improving medical imaging safety. I have written several quality measures on radiation dose adopted by the National Quality Forum and developed educational tools to help physicians and patients understand the importance of minimizing radiation exposure from imaging.

Prior to providing my opinions on the association between talcum powder products and ovarian cancer, I had not reviewed the relevant literature and had not published in this area. As a result, I brought an unbiased perspective to my review. This report reflects my review of medical and scientific publications in this area (overviews and scientific studies), my own analysis, and review of documents shared with me by the lawyers who engaged me for this task. My curriculum vitae is attached as Exhibit A, the materials I considered are attached as Exhibit B, and my fees and prior testimony are attached as Exhibit C.

III. Background: Ovarian cancer and Talc as a Modifiable Risk Factor

Ovarian Cancer

Ovarian cancer is the seventh most common cancer in women and the fifth leading cause of cancer deaths in the United States.¹ In 2018, 22,240 women are expected to receive a new diagnosis of ovarian cancer and 14,070 women will die from it. Overall, about 1 in 78 women (1.3%) will be diagnosed with ovarian cancer in their lifetime and around 1 in 108 will die of it. About 224,940 women are currently living with ovarian cancer.² Most cases occur among older women; the median age at diagnosis is 62, although this varies by ovarian cancer type.² Ovarian cancer is frequently diagnosed at a late stage, when a cure is unlikely. Because so many ovarian cancers are diagnosed at a late stage, the overall mortality rate is high, and the overall 5-year survival is poor. With the poor prognosis and absence of a reliable screening test to find ovarian cancer early, it is a highly feared cancer for women and their physicians alike.

Histologic types

Cancers are classified by histologic type, meaning the type of cells that are involved. Understanding ovarian cancer histologic types is important because the risk factors, etiology and genetics of ovarian cancer can vary by histological type. Therefore, the importance of talcum powder products as a risk factor or cause can also vary by type.

Ovarian cancers (epithelial and non-epithelial) are a heterogeneous group of malignancies that vary in their pathological appearance, molecular biology, risk factors, etiology and prognosis.¹ Epithelial ovarian cancers have several histologic types; most fall into a small group of more common types including serous, endometrioid, clear cell and mucinous. About 90% of ovarian cancers are epithelial (meaning they arise from cells on the surface of the ovary or fallopian tube) and the most common type of epithelial cancer is serous carcinoma. Serous is not only the most common type of ovarian cancer, it is also the most lethal type of ovarian cancer. Further, it is the type of cancer that pathologists can most consistently, reliably, and reproducibly diagnose. Thus, epidemiological studies will have the greatest ability to document a clear association between serous ovarian cancer types and talcum powder products, if a connection exists. It is also the subtype that has been studied most from a molecular and pathologic research standpoint.

Table 1. Histologic Types of Ovarian Cancers Diagnosed Over 15 Years at the KP Washington (in press, JAMA Internal Medicine)		
Histologic Type	Number	Percent of Total Cancers
Papillary serous cystadenocarcinoma	52	36.6
Endometrioid carcinoma	17	12.0
Serous cystadenocarcinoma	15	10.6
Clear cell adenocarcinoma	12	8.5
Adenocarcinoma, NOS	11	7.7
Mucinous adenocarcinoma	7	4.9
Mixed cell adenocarcinoma	3	2.1
Serous surface papillary carcinoma	3	2.1
Granulosa cell tumor	3	2.1
Carcinoma, not otherwise specific	2	1.4
Mucinous cystadenocarcinoma	2	1.4
Mucinous cystic tumor of borderline	2	1.4
Carcinoma in situ	1	0.7
Squamous cell carcinoma	1	0.7
Papillary adenocarcinoma	1	0.7
Papillary serous cystadenoma, borderline	1	0.7
Adenocarcinoma with squamous meta	1	0.7
Granulosa cell tumor, malignant	1	0.7
Endometrial stroma sarcoma	1	0.7
Mullerian mixed tumor	1	0.7
Carcinosarcoma	1	0.7
Carcinosarcoma, embryonal	1	0.7
Teratoma, malignant	1	0.7
Astrocytoma	1	0.7
Marginal zone B-cell lymphoma	1	0.7
Total	142	100
Summary		
Serous carcinoma	70	49.3
Endometrioid carcinoma	17	12.0
Clear cell carcinoma	12	8.5
Mucinous carcinoma	9	6.3

My research group recently reported on the ultrasound appearance of ovarian cancers among a large cohort of women. The purpose of this cohort study was to quantify the risk of malignant ovarian cancer based on ultrasound findings. We described 142 new ovarian cancer cases in a population of 500,000 women enrolled in Kaiser Permanente Washington, an integrated health plan, between 1997 and 2008, including 72,093 women who underwent pelvic ultrasound. The distribution of cancer histological types is in Table 1. Serous carcinoma was the most common cancer type: In our cohort, it was 50% of the ovarian cancers. Serous carcinoma has the worst prognosis of the ovarian cancer types. Its high frequency and poor

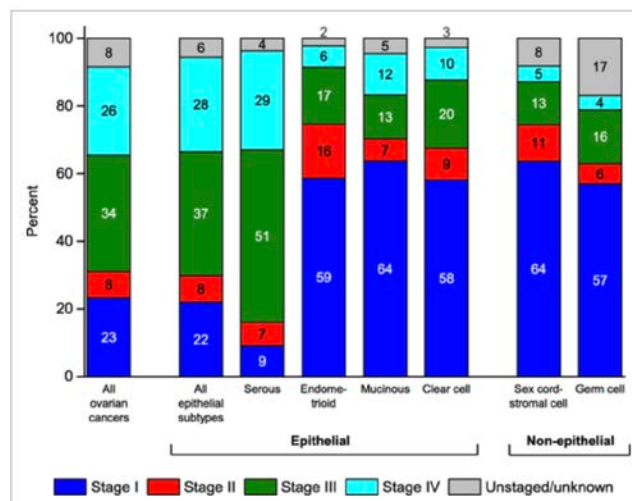
prognosis contribute to the high mortality rate for ovarian cancer overall. The other common histological types of ovarian cancer were endometrioid (12% in our data), clear cell (8.5% in our data), and mucinous (6.3% in our data).

Ovarian cancer types have large differences in stage of diagnosis (a strong predictor of survival) and prognosis independent of stage. The 5-year survival by histological type is in Table 2. Serous cancer is the most frequent and most aggressive, with an overall 5-year survival of 43% as compared with 82% for endometrioid. The survival is strongly influenced by stage at diagnosis, with higher stage numbers indicating more advanced stage.¹ Most serous carcinomas are diagnosed at stage III (51%) or IV (29%) (Figure 1),² for which 5-year survivals from the most recent data were 42% and 26%, respectively. These data reflect the aggressive nature of serous cancer.¹ In contrast, the majority (58% to 64%) of endometrioid, mucinous, and clear cell carcinomas are diagnosed at stage I, similar to nonepithelial tumors (Figure 1). Consequently, the 5-year survivals are 82%, 71%, and 66%, respectively, for endometrioid, mucinous, and clear cell carcinoma. Thus, these cancers behave very differently, even though all are ovarian epithelial cancers.

Table 2. Percent of Women Surviving 5 Years After Diagnosis by Epithelial Ovarian Cancer Type. Data From 2008–2013.

	All epithelial types	Serous	Endometrioid	Mucinous	Clear cell	Sex cord-stromal	Germ cell
Stage							
All	47	43	82	71	66	88	94
Stage I	89	86	95	92	85	98	99
Stage II	71	71	84	69	71	84	93
Stage III	41	42	59	30	35	61	90
Stage IV	20	26	29	13	16	41	69

Figure 1. American Joint Committee on Cancer Sixth Edition Stage Distribution (%) for Ovarian Cancer by Histology, US, 2007-2013, SEER 18 Registries, NCI, 2017. This shows that serious cancers are more likely to be diagnosed at state III, IV (green and teal), compared with other tumor types.



This summary reflects our current knowledge about ovarian cancer histologic types and their associated prognoses. As research results are reported, our knowledge will evolve. For example, recent studies suggest we need to improve our ability to distinguish between high-grade serous and endometrioid carcinomas. Other results suggest that many ovarian mucinous carcinomas are actually gastrointestinal tumors that metastasized to the ovaries and this realization is affecting the reported rates of ovarian mucinous carcinomas (which are declining).^{1,3,4} The categorization of noninvasive tumors classified as borderline is also under investigation and a topic of discussion in the field. These noninvasive tumors have historically been considered in the spectrum of ovarian cancer that have less aggressive behavior. However, many previously described borderline cancers are now generally considered non-malignant.

In summary, when assessing the carcinogenicity of talcum power products, this should focus on invasive serous carcinoma as the most important cancer (based on prognosis) and the most reliable cancer to identify (based on histology and understanding of cancer behavior).

Additionally, over the last decade, there has been research suggesting that many ovarian cancers originate from cells in the distal portion of the fallopian tube. Because the pathogenesis, treatment, and prognosis of serous cancers of the fallopian tube, ovary, and peritoneum are similar, these are now typically considered as a single entity.⁴ This consideration applies to the association with talcum powder product usage discussed in this report.

Risk Factors

Understanding ovarian cancer risk factors is important because analyzing the impact of talcum powder products exposure must consider *covariates, or other characteristics* that a woman might have that might also influence her ovarian cancer risk such as age, inherited genetic mutations, reproductive factors, or family history of cancer. Every risk factor does not have to be considered to come to a valid conclusion; indeed, this is not realistic within the limitations of medical research, and the bias introduced by the exclusion of some risk factors will be small. However, crude analyses that look at the risk of ovarian cancer from talcum powder products without adjusting for any other risk factors must be considered cautiously. For that reason, statistical analyses of research results often adjust for *confounding factors or variables that are covariates that hinder accurate calculation of an association*, for example between talcum powder products and ovarian cancer.

Numerous risk factors are identified for ovarian cancer.⁵ Unfortunately, few can be modified by therapies or lifestyle changes. Risk factors vary by histologic type⁵ but those that increase risk of ovarian cancer include personal or family history of ovarian or breast cancer, inherited mutations including BRCA1 and BRCA2⁶⁻¹⁰ advanced age, white race, increased education, and endometriosis. Other factors that may increase ovarian cancer risk due to estrogen exposure include having no pregnancies or advanced age at first birth, obesity, and postmenopausal hormone therapy.¹¹⁻¹³ Several factors are associated with reduced risk for ovarian cancer including breast feeding, multiple pregnancies, use of oral contraception,

tubal ligation, and removal of uterus, fallopian tubes, or both. ¹⁴⁻¹⁸ Smoking is a possible risk factor for ovarian cancer, primarily mucinous subtype, although study results have not been consistent. ^{5,19}

Risk factors vary by cancer type. For example, serous cancer is more strongly associated with reproductive risk factors than mucinous tumors ²⁰⁻²² and different histologic types have different molecular and genetic profiles. ²³⁻²⁵ Serous tumors are more likely to have a cancer-promoting mutation in the p53 gene, whereas similar KRAS mutations are more common in mucinous tumors. Over time, the occurrence of ovarian cancer has changed, in part due to changes in risk factors. For example, small declines in the rates of endometrioid and serous cancer are attributed to declining use of hormone replacement among postmenopausal women.

Etiology: Origins, Causes, Development and Inflammation

Our understanding of the etiology and course of ovarian cancer continues to evolve. Hereditary genetic predisposition increases risk, but overall, accounts for only a small proportion of cancers. And even in women with hereditary genetic mutations, not all will develop ovarian cancer. The majority of ovarian cancers are now believed to arise in the distal portion of the fallopian tube. By convention, fallopian tube, ovary and peritoneal cancers are considered as a single entity. The most widely accepted mechanism for initiation, promotion and progression of ovarian cancer is tissue inflammation leading to a series of responses that result in cancer.

There is very clear and extensive scientific literature describing the relationship between inflammation and cancer across many anatomic areas. Chronic inflammation, and even subtle, subclinical inflammation, is associated with an increased risk of cancer. ²⁶⁻²⁸ Many inflammatory conditions predispose to cancer development. Diverse factors that lead to inflammation - infection, chemical exposures, physical agents, autoimmune factors, and even inflammatory reactions of uncertain etiology - can lead to an increase in cancer incidence. For example, there are well described and accepted causal pathways linking inflammation in the etiology of bladder cancer (schistosomiasis, toxic chemicals), cervical cancer (papillomavirus), gastric cancer (H Pylori), colon cancer (inflammatory bowel disease), liver cancer (hepatitis), mesothelioma (asbestos) and ovarian cancer (pelvic inflammatory disease and endometriosis). The biological pathways associated with inflammation include stimulation/interference with a range of biological responses that are involved in initiation of cancer, promotion of cancer, and progression of cancer. Oxidative stress resulting from inflammation can impact all stages of cancer development including cancer initiation (DNA is damaged by introducing gene mutations and structural alterations of DNA leading to inhibition of DNA repair and malignant transformation); promotion (which may be manifest as abnormal gene expression resulting in cell proliferation and decrease apoptosis) and progression (further DNA damage and enhancement of cell growth. ²⁹ Local inflammatory response can lead to signaling molecules such as cytokines, chemokines, prostaglandins, growth transcription factors, microRNAs having higher expression that can promote cancer

development and can create a favorable microenvironment for the development and progression of cancer.³⁰ Inflammation impacts every step of tumorigenesis, from initiation through tumor promotion, and extending to metastatic progression. Similarly, the most compelling mechanism for the etiology of ovarian cancer is that of chronic inflammation and scarring in the ovary that leads to malignant transformation and cancer progression. This mechanism involves cell proliferation, oxidative stress, DNA damage and gene mutations.³¹⁻³³ The microenvironment of ovarian cancer contains a broad spectrum of pro-inflammatory cytokines and chemokines contributing to the mechanism.³⁸

There are many processes that can lead to inflammation and tumorigenesis and the exposure to talcum powder products is one such exposure that can strongly enhance the tumor promotion or progression as seen in in vitro and animal studies. For example, normal repeated ovulation leads to injury of ovarian epithelial cells and transformation to malignant cancer cells that can be enhanced by various factors such as talc or asbestos particles. Exposure to talcum powder products can induce the production of pro-oxidant enzymes and reduced production of antioxidant enzymes leads to malignant transformation. In support of inflammation from talcum powder products causing cancer, hysterectomy or bilateral tubal ligation, which would significantly limit ovarian exposure to inflammatory mediators, and toxins, is associated with reduced ovarian cancer risk.

Relationship Between Ovarian Cancer and Talcum Powder Products

The epidemiological evidence described in detail below demonstrates a strong and positive association between exposure to talcum powder products and ovarian cancer and that talcum powder products cause ovarian cancer. Although epidemiologic evidence alone does not provide a definitive mechanism or pathophysiological process that accounts for the increased risk, the evidence for inflammation as described above is very strong. Similarly, epidemiological evidence alone does not confirm the specific component or ingredient in talcum powder products that is responsible for its carcinogenesis. Nonetheless, several constituents within talc powder products are worth highlighting as they may be acting individually or together to create the carcinogenicity of talc powder products inasmuch as they are individually highly carcinogenic

Why Talcum Powder Products were Initially Suspected as Causing Ovarian Cancer

In 1978 samples of commercial body powders were shown to contain asbestos silica minerals. Asbestos was a known carcinogen and about half of the powder samples contained respirable quartz, a lung carcinogen. Concerns were primarily raised that inhaled powder could cause lung scarring, lung cancer, or mesothelioma. In 1971, Henderson observed talc particles deeply embedded in ovarian cancer tissue. The authors noted the close association of talc to the asbestos group of minerals.³⁹ Further concern was raised, in 1982 when a case-control study of ovarian cancer that collected information on talcum powder use reported an increased risk with perineal dusting.⁴⁰ These findings were reported in widely circulated newspapers such as The Globe, raising concern that the powders were carcinogenic because

of the contamination with asbestos, using the relationship between asbestos and lung cancer and mesothelioma as the basis for the concern.

Carcinomic of Constituents of Talc Powder Products

There are hundreds of different constituents and ingredients within talcum powder products in addition to platy talc. Many of these are Group 1 carcinogens (such as asbestos, talc containing asbestiform fibers, heavy metals, and some fragrance chemicals) that likely contribute to the carcinogenicity of the products.

Asbestos

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers; serpentine mineral fibers are called chrysotile, and amphibole minerals include actinolite, amosite, anthophyllite, crocidolite and tremolites. Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition. Small amounts of chrysotile (asbestos) may occur in these talc deposits^{41,42} When talc is mined it may contain asbestos fibers^{42,43} A study of 21 consumer talcum powders obtained from retail stores in 1971–1975 reported that 10 contained concentrations of asbestos fibers ranging from 0.2 to 14%.^{41,44} Because of concern that asbestos was present in talcum powder products and the known carcinogenicity of asbestos, it has been reported that voluntary guidelines were established by the cosmetic industry in 1976 to limit the content of asbestos fibers in commercial talc preparations. While currently talcum powder products are believed to free from asbestos, the data on its continued presences are strong. I have seen evidence of continued presence since 1976.⁴⁵⁻⁴⁸ For example, Longo tested approximately 50 samples that were taken between the years 1960 through 2000 and the majority of sample are positive for asbestos.⁴⁷

Asbestos is a known and potent human carcinogen. Asbestos is highly carcinogenic to the lungs, lining of the lungs, and larynx.⁴⁹ Asbestos is also highly carcinogenic to the ovaries.⁴⁹⁻⁵⁸ Women working in asbestos-manufacturing industries have an increased risk of ovarian cancer. IARC reviewed the association between asbestos exposure and ovarian cancer in 2012. To assess the relationship, IARC reviewed data primarily from large epidemiological cohort studies of women who had occupational exposure to asbestos as well case-control studies on non-occupational exposure. The context and lengths of exposures varied, along with the type of asbestos fibers to which the women were exposed and the study designs and assessments. Nonetheless, the results were consistent. Most, but not all, were statistically significant and documented a strong and compelling causal association between exposure to asbestos and ovarian cancer, largely the result of the association from cohort studies of women with substantial occupational exposures.⁵⁰⁻⁵⁴ **IARC concluded that there is sufficient evidence that asbestos is carcinogenic in humans and that asbestos causes cancer of the ovary.** This is the highest risk category.⁴⁹ IARC also concluded that this categorization applied to all forms of asbestos and to talc containing asbestiform fibers (talc in a fibrous habit or fibrous talc)). IARC also concluded that asbestos is carcinogenic based on animal studies. Camargo completed a systematic review of the relationship between women occupationally exposed to asbestos and ovarian cancer.⁵⁹ The authors found that of the 18 cohort studies

the pooled standard mortality estimate for ovarian cancer was 1.77 (95% confidence interval, 1.37-2.28). The range in reported SMR values was 1.1– 5.4 across the included cohort studies and the most common values were 2–3. This study supports IARC's conclusion that exposure to asbestos causes ovarian cancer.

IARC explicitly stated that the findings in this Monograph applied to all forms of asbestos, as well as asbestiform talc (fibrous talc).

I reviewed many publications and primary research studies, including experimental and basic science models showing molecular and genetic cancer-promoting changes to cells that occur from exposure to asbestos fibers. I also strongly conclude that asbestos causes ovarian cancer.

Talc

Talc is the primary component of talcum powder products. The chemical structures of talc and asbestos can be similar. While talc particles are usually plate-like, talc can also grow as a fiber which is similar to the group of minerals called asbestos. Both are magnesium silicate and when talc has the fibrous form it is called asbestiform because of its similarity to asbestos. The form of the talc fibers is long and thin, with parallel bundles that are easy to separate from each other, and closely resembles the physical appearance of asbestos minerals. The histologic appearances of mesothelioma and ovarian cancer are similar. The known carcinogenicity of asbestos for lung, pleural, peritoneal and ovarian cancer has led to the theory that the similarity in the fibers and the resulting cancers suggests that talc works mechanistically within the ovary to induce cancer in a way that is similar to how asbestos in the chest induces mesothelioma.

Early observations demonstrated talc particles in both malignant and normal ovaries establishing a route from the perineum to the ovary and shows that many women are exposed to talc.^{39,60} In 2006, the International Agency for Research on Cancer (IARC) reviewed the data on cosmetic (perineal) talc ("non-asbestiform") application and concluded that it is possibly carcinogenic to humans.⁶¹ This is not as strong a recommendation as they made for asbestos and ovarian cancer, but nonetheless is a strong recommendation. IARC classified genital-perineal use of talc-based powder as possibly carcinogenic. Exposure to talc particles can induce an inflammatory response, either directly at the ovary and ovary-fallopian tube juncture, causing local irritation from talc particulates or through more generalized peritoneal inflammation. The mechanism that can lead to cancer is local irritation by talc fibers that disrupts the epithelial surface, increasing rates of cell division and DNA repair that can lead to mutations. Also increased are oxidative stress and cytokine production, indicating inflammation. Fibers that are incorporated into the epithelial cells enter ovarian tissue. This inflammation initiates a series of responses, supported by research, that promote cancer. The reduction in the elevated risk of ovarian cancer from talcum powder exposure after hysterectomy or tubal ligation supports the mechanism by which local irritation and inflammation to the ovary from talc or asbestos causes an elevated cancer risk.

Heavy Metals

Talc powder products can contain Group 1 metals that are considered by IARC as carcinogenic to humans. ^{44,49}

This includes nickel compounds which IARC documents cause lung and nasal cavity and paranasal sinus cancer. (IARC100c-10, 2012). Nickel compounds “cause DNA damage, chromosomal aberrations, delayed mutagenicity and chromosomal instability ... and nickel compounds act as co-mutagens.” Talcum powder products also contain Chromium (VI) (IARC100c-9, 2012) another Group 1 carcinogen, where there is sufficient evidence in humans for carcinogenicity (to the nose and nasal sinus). The mechanism includes “DNA damage, generation of oxidative stress and aneuploidy. Talc powder products can also contain Group 2A metals that are considered probably carcinogenic to humans, such as Cobalt which can be found in talc powder products. ⁶² IARC considers Cobalt metal with tungsten carbide as probably carcinogenic to humans (Group 2A), but worth noting that a number of the IARC working group members supported an evaluation in Group 1 because they judged the epidemiological evidence to be sufficient, leading to an overall evaluation in Group 1; or they judged the mechanistic evidence to be strong enough to justify upgrading the default evaluation from 2A to 1. The majority of working group members, who supported the group 2A evaluation, cited the need for either sufficient evidence in humans or strong mechanistic evidence in exposed humans. Cobalt metal without tungsten carbide is also considered possibly carcinogenic to humans (Group 2B). Cobalt sulfate and other soluble cobalt(II) salts are possibly carcinogenic to humans (Group 2B).

Any and all of these heavy metals can cause ovarian cancer through an inflammatory mechanism

Fragrances

There are more than 150 different chemicals added to Johnson’s Baby Powder and Shower to Shower products. I reviewed the expert report from Dr. Crowley that concludes that some of these chemicals may contribute to the inflammatory response, toxicity, and potential carcinogenicity of Johnson & Johnson’s talcum powder products. I concur with his opinion. ⁶³

IV. Overview of Publications on Genital Use of Talc Powder Products and Ovarian Cancer

To understand the relationship between exposure to talcum powder products and ovarian cancer, I searched for and reviewed scientific papers on this topic. I used several searchable publication databases (Scopus, Embase, Pubmed) and manually searched the reference lists of all articles I found, including a large number of reviews. The results of my review follow the explanation of the main types of studies and articles.

Explanation of study designs and article types

Nearly all published studies that I reviewed used one of two designs: case-control and cohort. Each design has strengths and biases. The commonly held view is that cohort studies are better than case-control studies. This is a misconception thus it is worth explaining their differences. Many articles I reviewed were systematic reviews, which are also explained.

Case-control studies compare people with a condition (cases) by matching them to people with similar characteristics who do not have the condition (controls) to determine the effect of a potential disease-causing factor. They often analyze existing data retrospectively, after people have been diagnosed, and involve tens or hundreds of patients. Cohort studies compare cohorts, or groups of people, who were exposed or not exposed to a potential disease agent. They often collect data on people prospectively, before they develop a disease and track their health over time. Both case-control and cohort studies, if well done, can provide accurate and meaningful information about statistical associations. In general, however, the risk of bias is greater for case-control studies. (An example is recall bias, in which women are more likely to remember and report exposure to talc powder products after they have been diagnosed with cancer compared to women without a diagnosis, perhaps because diagnosed women heard that talc powder products is harmful and are more likely to remember talc use). Nonetheless, when studying a rare disease, the case-control design is frequently highly efficient and desirable as it allows you to assemble a much larger number of cases and can delve in great depth for particular exposures. You can identify all patients who have the outcome of interest, and then query them (and some control group) about any antecedent exposure. The identification of the control group is very important. My large, National Institutes of Health-funded study of cancer risk factors in children is employing a case-control design. This design permits us to ask very detailed questions of a small number of individuals about their various exposures.

Cohort studies potentially avoid some biases of case-control studies since exposures are prospectively assessed and quantified, that is, before disease outcomes. This design also has limitations, though. An extremely important limitation is that because cohort studies are expensive and time-consuming, they rarely focus on a single, narrowly defined question such as the association between regular use of talcum powder products and cancer. Usually, researchers investigate a broad range of questions in cohort studies, so asking patients in-depth questions about any given topic is difficult, especially since tens of thousands of patients may be surveyed on many topics. Further, in cohort studies, having comprehensive assessment of outcomes on all individuals in the cohort is extremely important. Losing patients to follow up (meaning researchers cannot contact or find records on a participant) leads to study bias. The other disadvantage of cohort studies is that a very large number of patients must be assessed over a long period of time to see who will develop a rare outcome (like ovarian cancer). Because of this, typically there will be far fewer patients with disease in a cohort study as compared with case control study (like in this case).

The small number of cohort studies I found on the relationship between talcum powder products exposure and ovarian cancer did not focus on the details of this topic. While they may have included questions about talcum powder exposure, they were not sufficiently nuanced to provide meaningful information. Thus, in most of the cohort studies I found, measurements of exposure were poor, not specific, or inaccurate. Further, several had very short follow-up periods with data or information about the time before the cancer occurred. This negates an advantage of cohort studies, which is being able to learn about exposures before the cancer, eliminating recall bias.

Systematic reviews quantitatively summarize results across multiple studies. One of the rationales of this study design is that individual studies may not have enough participants to yield meaningful results because they are too small or insufficiently powered. Combining small studies can provide more stable and reliable summary estimates of the effects of disease agents and risk factors. Further, a systematic review may be better than a single study, as it provides broader evidence of the results and includes patients from diverse settings. However, in order to statistically combine and summarize the data from different research studies into a single systematic meta-analytic review, the combined studies must ask the same research question and follow sufficiently similar and rigorous scientific methods. A meta-analysis does not compensate for gaps or flaws in an original study: Combining three poorly performed studies does not yield reliable summary estimates even though there may be three times the number of patients. Similarly, combining studies that ask different research questions (for example, assessing women of different ages for a disease in which age is an important risk factor) does not provide reliable summaries. Results from different studies often vary when the studies ask different research questions, have different criteria for including participants, or use different methods. I raise these issues to point out that systematic reviews must be read extremely carefully to ensure that their conclusions are valid.

Table of Reviewed Publications

I identified and reviewed 43 English-language publications that provided quantitative data based on epidemiological studies about the relationship between genital talcum powder exposure and ovarian cancer (Table 3). This list includes 4 cohort studies, 8 systematic meta-analytic reviews, 2 studies that pooled individual patient-level data from several research studies, and 30 case-control studies. One study contributed both the systematic review and a case control study. I also read multiple review articles that are not included in the table. The epidemiological studies were published between 1982 and 2018. I have described the results organized by study design below.

Most studies used a case-control study design with a small number using a cohort study design. Although some studies assessed powder use to any part of the body or assessed the use of talcum powder on diaphragms, condoms or sanitary napkins, the primary research question that I focused on in my review and that was assessed in all included individual research studies, was whether genital area exposure to talcum powder increases risk of epithelial ovarian cancer. Occasionally, study authors assessed combination exposures (i.e., to genitals and other body parts). These studies were included as long as genital powder use was assessed. Nearly all studies adjusted for known ovarian cancer risk factors, but those factors varied. The vast majority of studies found a positive association between any exposure to talcum powder products and cancer. However, the sample size of some studies was small and resulted in high statistical uncertainty. Because of these and other limitations, quantifying a precise association between exposure and cancer was difficult from my review of the literature. The data for some studies may have shown that effects of talcum powder exposure (measured as odds ratios, ORs) was meaningful for cancer development, but with statistical

uncertainty; whereas other studies showed the reverse results, with ORs not showing a positive association, but statistical parameters suggesting that a meaningful association was nonetheless possible because of wide confidence intervals. Therefore, I thought a more precise and careful review was called for. The number of individual women included in each study and the reported or estimated effect size for “any exposure to talc” (adjusted for other risk factors such as age) are in Table 4.

A subset of the studies quantified the *intensity (frequency)* of each woman’s exposure to talc to assess the importance of use patterns (e.g., if a single lifetime use or weekly, monthly, or daily use increased ovarian cancer risk) or *dose dependency (links between the number of exposures and cancer risk, e.g., if doubling exposure doubles risk)*. Further, a subset of studies stratified by cancer type (invasive vs. low malignant potential/borderline) and whether the risks varied by histological types including the four dominant types of serous, mucinous, clear cell, and endometrioid cancer.

Studies that provided data on the frequency of talc use and association by histologic type were included in a separate systematic meta-analytic review that I conducted as part of my review of the literature to include in this report. The reason I completed my own statistical review is further explained below.

Quantifying Exposures

A large proportion of women will have used talcum powder products, highlighting the importance of this issue. However, publications that focus on women reporting “any” genital exposure to talc (i.e., talc at any point in life and for any duration) may be too broad to provide meaningful information. For example, “any use” will include women who applied talc powder products three times over five decades and women who used talc powder products daily, whose might have had 20,000 applications and exposures in comparison to three. Defining a variable as any use is the equivalent to creating a variable of any smoking use, that combines data on individuals who tried one cigarette in their life with individuals with 50 pack years of tobacco use. Combining data on women with infrequent or sporadic exposures with data from women with frequent, sustained use leads to imprecise results, masking any causal associations. Therefore, I selected the studies for my own review that quantified the frequency of talc powder products use as having the most informative data and included them in a separate systematic review.

Summary of Data

I grouped the research studies by their study design. What follows is my review of the cohort studies, systematic review studies, pooled data studies, followed by my own review.

Cohort Studies

Four cohorts (Gertig, Gates, Houghton, Gonzalez) have been published on talcum powder products and ovarian cancer.

Cohort 1: Gertig (2000) ⁶⁴

This first cohort study assessed the relationship between perineal talc and ovarian cancer within the context of the US Nurses' Health Study, a prospective study of 121,700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. These are mostly premenopausal women. While talc exposure was not an initial part of the study, questions about talc, including measuring frequency of exposure, were added in 1982; a large subset of the cohort (78,630 women) completed these questions and were included in analyses. Among these women who were followed for 14 years, 307 were diagnosed with epithelial ovarian cancer. After adjusting for confounding variables, the *relative risk (RR)* of developing ovarian cancer (*the likelihood of ovarian cancer in talc users compared to nonusers, with higher RR meaning increased risk stronger association*) among daily users of talc was RR 1.12 (95% confidence interval [CI] 0.82, 1.55, *a measure of statistical uncertainty, with wider ranges indicating greater uncertainty*), which was not statistically significant. However, when results were classified by histologic subtype, the RR of invasive serous cancers was significantly elevated among any users of talc (RR 1.40, 95% CI 1.02, 1.9) and the RR of invasive serous cancer among daily users of talc was higher at RR 1.49 (95% CI 0.98, 2.3).

In this cohort study, the researchers assessed talc exposure before cancer diagnosis, avoiding the possibility of the recall bias of case-control studies. This was a strong strength of this study. A potential weakness was that frequency (i.e. daily) but not duration (number of years) of talc use was measured, so a clear lifetime exposure measure was missing. The researchers nonetheless quantified exposure at the time the talc questions were asked, which was probably strongly associated with prior use (i.e. an approximation on ongoing use). **This study provides strong evidence that perineal exposure to talc increases the risk of invasive serous ovarian cancer, particularly among daily users of talc, with about a 50% increased risk,** which is substantial and meaningful.

Cohort 2: Gates (2010) ²⁴

This study assessed the association between ovarian cancer risk factors and incidence of ovarian tumors by histological type using data from the US Nurses' Health Study combined with data from the Nurses' Health Study II, which included a second period of enrolling participants. Unfortunately, talc use was assessed only on the first survey and not assessed among patients enrolled in the Nurses' Health Study II. Thus, this extends the period of follow up from the initial NHS but does not include greater information about risk factors. Results were presented for any talc powder products use and not for frequency of use. **Thus, this report does not add to a meaningful assessment of the relationship between talc use and ovarian cancer because it used exactly the same patient group as Gertig (2000) but provided less information to quantify the frequency of talc use.**

Cohort 3: Houghton (2013) ⁶⁵

This study assessed perineal talc powder products use and risk of ovarian cancer in the Women's Health Initiative Observational study, in which postmenopausal women aged 50–79 were enrolled in a prospective cohort of women from 40 clinical centers across the United

States in 1993–1998. Overall, 61,576 women were included in analyses, including 429 diagnosed with ovarian cancer. Perineal powder use was assessed at the start of the study. Participants were asked if they **ever used talc powder products** on their private parts (genital areas). Those who responded yes were asked about duration (years) of use. Women were followed for a mean of 12 years and the median age of participants was 63. **Talc powder products use was associated with a 12% increase in risk of ovarian cancer after accounting for covariates** (RR 1.12, 95% CI 0.92, 1.36). When limited to women who used perineal powder for 20 years or more, the RR was 1.10 (95% CI 0.82, 1.48). When limited to serous ovarian cancer, the RR was 1.13 (95% CI 0.84, 1.51.) **The primary limitation of the study was that frequency of talc powder products use was not assessed—and thus the authors could focus only on any talcum powder use.** The imprecision in estimation of talcum powder exposure makes the results not terribly meaningful. The second limitation was the relatively short follow-up of 12 years to identify ovarian cancer diagnoses.

Cohort 4: Gonzalez (2016) ⁶⁶

The Sister Study (2003–2009) followed 50,884 women ages 35 to 75 years in the US and Puerto Rico who had a sister diagnosed with breast cancer. After excluding participants who had bilateral oophorectomies, ovarian cancer, or were lost to follow-up, 41,654 participants were included. At baseline participants were asked about douching and talc use during the previous 12 months, and during follow-up (median of 6.6 years) 154 participants reported a diagnosis of ovarian cancer. The authors computed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for ovarian cancer risk using the Cox proportional hazards model. The authors found no significant association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73 CI: 0.44, 1.2). **The primary limitations of this study are that the authors combined a large number of potential talc exposures into a single category, including genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Further, the authors categorized the exposure based on the 12 months prior to enrollment as a dichotomous ever/never.** Thus not only was it an ever versus never category, the ever category was extremely broad, making the lack of association less meaningful. Further, there are several other factors that make the results questionable, including lower than expected proportion of women who report any exposure to talc powder products, and the lack of a validated approach to ascertainment of ovarian cancer.

Cohort Studies: Summary

Analyses of data from the US Nurses' Health study and the Women's Health Initiative estimated that women who report any exposure talc powder products will have a 12% increase in ovarian cancer compared to women who never report talc powder products use, although this estimate was not statistically significant. The primary limitation of this estimate is that it is based on *any talc powder products* use, which is a weak, crude predictor. Similarly, while the results from the Sisters study did not identify a significant association between talc powder products use and ovarian cancer, they too used a measure of ever use, and included a large number of different types of exposures that would not be expected to measure a single exposure. The most important and meaningful conclusion that I draw from the cohort studies

is from the Gertig 2000 study using data from the US Nurses' Health study: That women who are **daily users of talc have an approximately 50% increase (OR 1.49) in their risk of invasive serous** cancer, the most lethal and frequent type of ovarian cancer.

Systematic Reviews

I found nine systematic reviews that summarized the relationship between talc and ovarian cancer, summarized below. These reviews were completed using various subsets of the full list of publications. The systematic reviewers are presented with the most recent first, because the more recent studies tended to be more complete, comprehensive and the most methodologically rigorous.

Systematic Review 1: Penninkilampi (2018) ⁶⁷

This comprehensive systematic review of the association between any genital use of talcum powder products and ovarian cancer conducted a stratified analyses showing the association by frequency of talc use and histologic cancer subtype. The methods of the study are well described. The researchers identified studies using six electronic databases and reviewed publications with 50 or more cases of ovarian cancer. They identified 24 case-control studies describing 13,421 cases and the three cohort studies (890 cases, 181,860 person-years) described above. Any reported use of perineal talc powder products was associated with increased risk of ovarian cancer compared to no use (OR = 1.31; 95% CI 1.24, 1.39). Women with more than 3600 lifetime applications had slightly higher risks (OR = 1.42; 95% CI 1.25, 1.61). Women who reported long-term (>10 years) talc use also had an increased risk (OR 1.25; 95% CI = 1.10, 1.43). The association between any talcum powder product exposure and ovarian cancer was limited to studies that used a case-control design. The cohort studies showed an increased risk of serous invasive cancer subtypes for perineal talc use compared to no use (OR = 1.25; 95% CI = 1.01, 1.55). While serous and endometrioid cancer were associated with talcum powder products use, no association was seen with mucinous or clear cell cancers. The review authors concluded, from the data, that perineal talcum powder use and ovarian cancer were consistently associated, with a slightly higher risk in women who report greater usage. Some variation in the magnitude of the effect of talcum powder products was found when considering the study designs and ovarian cancer subtypes. Several small methodological issues are that Penniniklampi may have included some groups of patients more than once in analyses and did not include updated data or previously unpublished data available from a research consortium on ovarian cancer. However, these concerns are unlikely to have had a significant impact on their estimates.

Table 3. List of Included Studies, sorted by study design

	Study Type	Year	Author	Journal	Title
1	Cohort Study	2000	Gerting	J Natl Cancer Inst	Prospective study of talc use and ovarian cancer (in the Nurses' Health Study)
2	Cohort Study	2010	Gates	Am J Epidemiol	Risk factors for epithelial ovarian cancer by histologic type; US Nurses Health Study
3	Cohort Study	2014	Houghton	J Natl Cancer Inst	Perineal powder use and risk of ovarian cancer: Results from the Women's Health Initiative
4	Cohort Study	2016	Gonzalez	Epidemiology	Douching, talc use and risk of ovarian cancer: Results from the Sister Study
5	Systematic Rev.	1992	Harlow	Obst Gyn	Perineal exposure to talc and ovarian cancer risk
6	Systematic Rev.	1995	Gross	J Expo Anal Env Epid	A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer
7	Systematic Rev.	2003	Huncharek	Anticancer Res	Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies
8	Systematic Rev.	2007	Huncharek	Eur J Cancer Prev	Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies.
9	Systematic Rev.	2008	Langseth	J Epid Community Health	Perineal use of talc and risk of ovarian cancer.
10	Systematic Rev.	2010	IARC	IARC Monographs	IARC monographs on the evaluation of carcinogenic risks to humans: Carbon black, titanium dioxide, and talc
11	Systematic Rev.	2017	Berg	European J of Can Prev	Genital use of talc and risk of ovarian cancer: A meta-analysis
12	Systematic Rev.	2018	Penninkilampi	Epidemiology	Perineal talc use and ovarian cancer: A systematic review and meta-analysis.
13	Pooled Data	2013	Terry	Cancer Prev Res	Genital powder use and risk of ovarian cancer: a pooled analysis of 8525 cases and 9859 controls
14	Pooled Data	2016	Cramer	Epidemiology	The association between talc use and ovarian cancer- A retrospective case- control study two US states
15	Case-Control	1982	Cramer	Cancer	Ovarian cancer and talc: A case control study
16	Case-Control	1983	Hartge	JAMA	Talc and ovarian cancer
17	Case-Control	1988	Whittemore	Am J Epidemiol	Personal and environmental characteristics related to epithelial ovarian cancer. Exposure to talcum powder, tobacco, alcohol, and coffee
5	Case-Control	1989	Harlow	Am J Epidemiol	A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc
18	Case-Control	1989	Booth	BR Cancer	Risk factors for ovarian cancer: a case-control study
19	Case-Control	1992	Harlow	Obstet Gynecol	Perineal exposure to talc and ovarian cancer risk
20	Case-Control	1992	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer
21	Case-Control	1992	Chen	Int J Epidemiol	Risk factors for epithelial ovarian cancer in Beijing, China
22	Case-Control	1993	Tzonous	Int J Cancer	Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer
23	Case-Control	1995	Purdie	Int J Cancer	Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study
24	Case-Control	1996	Shushan	Fertil Steril	Human menopausal gonadotropin and the risk of epithelial ovarian cancer
25	Case-Control	1997	Chang	Cancer	Perineal talc exposure and risk of ovarian carcinoma
26	Case-Control	1997	Cook	Am J Epidemiol	Perineal powder exposure and the risk of ovarian cancer
27	Case-Control	1998	Green	Int J Cancer	Tubal sterilization, hysterectomy and decreased risk of ovarian cancer.
28	Case-Control	1998	Godard	Am J Obstet Gynecol	Risk factors for familial and sporadic ovarian cancer among French Canadians: A case-control study
29	Case-Control	1999	Cramer	International J of Cancer	Genital talc exposure and risk of ovarian cancer
30	Case-Control	1999	Wong	Obstet Gynecol	Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study
31	Case-Control	2000	Ness	Epidemiol	Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer
32	Case-Control	2004	Pike	Fertil Steril	Hormonal factors and the risk of invasive ovarian cancer: A population based case control study
33	Case-Control	2004	Mills	Am J Epidemiol	Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California
34	Case-Control	2008	Goodman	Endocr Relat Cancer	Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk
35	Case-Control	2008	Gates	Cancer Epid Bio Prev	Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer
36	Case-Control	2008	Merritt	Int J Cancer	Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer
37	Case-Control	2009	Moorman	Am J Epidemiol	Ovarian cancer risk factors in African-American and white women
38	Case-Control	2009	Wu	Int J Cancer	Markers of inflammation and risk of ovarian cancer in Los Angeles County
39	Case-Control	2011	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer
40	Case-Control	2012	Lo-Cigna	Epidemiol	Aspirin, non-aspirin non-steroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer
41	Case-Control	2012	Kurta	Cancer Epid Bio Prev	Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study
42	Case-Control	2015	Wu	Cancer Epid Bio Prev	African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after considering nongenetic risk factors and oophorectomy rates
43	Case-Control	2016	Schildkraut	Cancer Epid Bio Prev	Association between body powder use and ovarian cancer: the African American Cancer epidemiology Study

Table 4. List of Included Studies with Number of Cancers, Controls, and Reported Odds Ratios

	Study Type	Year	Author	Cancers	Controls or Cohort Size	Odds Ratio	95% CI
1	Cohort Study	2000	Gerting	307	78,630	1.12	(0.82, 1.55)
2	Cohort Study	2010	Gates	797	108,073	1.06	(0.89, 1.28)
3	Cohort Study	2014	Houghton	427	61,576	1.12	(0.92, 1.36)
4	Cohort Study	2016	Gonzalez	154	41,654	0.73	(0.44, 1.2)
5	Systematic Review	1992	Harlow *	1,106	1,756	1.30	(1.1, 1.6)
6	Systematic Review	1995	Gross	1,333	2,362	1.29	(1.02, 1.63)
7	Systematic Review	2007	Huncharek	1,858	2,830	NA	NA
8	Systematic Review	2003	Huncharek	5,260	6,673	1.33	(1.16, 1.45)
9	Systematic Review	2008	Langseth			1.35	NA
10	Systematic Review	2010	IARC			1.30	
11	Systematic Review	2017	Berg	15,230	NR	1.22	(1.13, 1.30)
12	Systematic Review	2018	Penninkilampi	14,311	NR	1.31	1.24, 1.39
13	Pooled Data	2013	Terry	4,472	6,175	1.37	(1.19-1.58)
14	Pooled Data	2016	Cramer	2,041	2,100	1.38	(1.01, 1.99)
15	Case-Control Study	1982	Cramer	215	215	1.58	(0.98, 2.47)
16	Case-Control Study	1983	Hartge	135	171	2.50	(0.70, 10.0)
17	Case-Control Study	1988	Whittemoore	188	539	1.45	(0.94, 2.22)
5	Case-Control Study	1989	Harlow	116	158	1.10	(0.70, 2.1)
18	Case-Control Study	1989	Booth	235	451	1.30	(0.80, 1.9)
19	Case-Control Study	1992	Harlow	235	239	1.80	(1.1, 3.0)
20	Case-Control Study	1992	Rosenblatt	77	46	1.70	(.70, 3.9)
21	Case-Control Study	1992	Chen	112	224	3.90	(0.9, 10.6)
22	Case-Control Study	1993	Tzonous	189	200	1.05	(.28, 3.98)
23	Case-Control Study	1995	Purdie	824	860	1.27	(1.04, 1.54)
24	Case-Control Study	1996	Shushan **	200	408	2.00	NA
25	Case-Control Study	1997	Chang	367	564	1.51	(1.13, 2.02)
26	Case-Control Study	1997	Cook	313	422	1.60	(0.9, 2.9)
27	Case-Control Study	1998	Green	824	855	1.30	(1.1, 1.6)
28	Case-Control Study	1998	Godard	170	170	2.49	(0.94, 6.56)
29	Case-Control Study	1999	Cramer	563	523	1.60	(1.18, 2.15)
30	Case-Control Study	1999	Wong***	499	755	1.13	(0.89, 1.43)
31	Case-Control Study	2000	Ness	767	1,367	1.50	(1.1, 2.0)
32	Case-Control Study	2004	Pike				
33	Case-Control Study	2004	Mills	256	1,122	1.74	(1.14, 2.64)
34	Case-Control Study	2008	Goodman	367	602	0.99	(.70, 1.41)
35	Case-Control Study	2008	Gates			1.41	(1.14, 1.76)
36	Case-Control Study	2008	Merritt	1,576	1,509	1.34	(1.06, 1.68)
37	Case-Control Study	2009	Moorman	1,086	1,057	1.37	(1.05, 1.80)
38	Case-Control Study	2009	Wu	609	688	2.08	((1.34 3.23)
39	Case-Control Study	2011	Rosenblatt	812	1,313	1.13	(0.93, 1.36)
40	Case-Control Study	2012	Lo-Cignaie	902	1,802	1.34	(1.07, 1.66)
41	Case-Control Study	2012	Kurta	902	1,802	1.41	(1.16, 1.69)
42	Case-Control Study	2015	Wu	1,701	2,391	1.46	(1.27, 1.69)
43	Case-Control Study	2016	Schildkraut	584	745	1.71	(1.26, 2.33)

Odds ratio, likelihood (odds) that an outcome will occur because of a particular exposure compared to the likelihood it will occur without the exposure. 95% CI, 95% confidence interval, a measure of statistical uncertainty that says with about 95% of the time that the true value is within the range of numbers. The wider the range, the higher the uncertainty. NR, not reported.

* crude unadjusted estimate

** approximate, unadjusted estimate

*** assessed perineal or thigh use, and controls all have cancer

Berge (2018) ⁶⁸

This large, comprehensive systematic review of the association between genital use of talc powder products and ovarian cancer also had well-described methods. Berge reviewed and abstracted data for 27 publications and reported an overall summary estimate of the association between talc exposure and ovarian cancer. For six of the reviewed studies, Berge included data published in a pooled data analysis, from Terry ⁶⁹ described below) that had not been previously included in the original publications. Overall, data on 15,230 women with ovarian cancer were analyzed (a number that is incorrectly reported in the paper). This is slightly higher than the number included in Penninkilampi because of the additional patients from the Terry publication. The summary estimate for risk of ovarian cancer for women who ever used genital talc was RR 1.22 (95% CI 1.13, 1.30). When stratified by histologic type, serous carcinoma was the only type with a significant association to talc use (RR 1.24, 95% CI 1.15, 1.34). There was no difference in risk when tumors were categorized as invasive versus borderline.

To assess relationships among ovarian cancer and intensity and duration of use, these measures were analyzed separately rather than as a combined measure that would give an estimate of the total number of exposures; the analyses did not demonstrate a significant dose response. Importantly, these measures were assessed only in five studies with the results on frequency of use presented as increased risk per additional day per week of talc use, which assumes a very linear association. I was not able to identify the original studies used in the review that reported the results with this level of granularity. Because of the small number of studies, the results (3% increase in risk per additional day of talc used, with high statistical uncertainty) were not surprising.

The authors also stratified the results by the study design (as did Penninkilampi) and found that the association between talc exposure and ovarian cancer was significant only for the case-control studies, although, as above, the cohort studies had the weakest definition of exposure. The primary limitation of the review is defining exposure as ever having used talc. As described above, this is a broad, vague definition that probably dilutes any estimated association, as it includes both women with trivial use and with regular use. A second limitation is that the included studies adjusted for a variety of covariates although this is unavoidable in this type of summary. The large difference in general between adjusted and crude results emphasizes the importance of adjustments when estimating particular risk.

Langseth (2008) ⁷⁰

This systematic review of the association between genital use of talc powder products and ovarian cancer included 21 publications. The overall pooled odds of cancer were OR 1.35 across all studies. Several authors of this systematic review were involved in an IARC report on talc exposure. They analyzed a subset of eight studies used in the IARC report that were considered to be the most informative for estimating ovarian cancer risk. Analysis of these more relevant, higher quality studies, produced an increased ovarian cancer risk of 30 to 60% (presumably OR 1.3–1.6) associated with talcum powder use. This subset analysis did not document a dose response or assess associations by cancer types.

Huncharek (2007) ⁷¹

Huncharek summarized the results of nine studies that reported on the association between talc used on contraceptive diaphragms and ovarian cancer. No data on perineal talc exposure were analyzed and the data are not included herein. Of note, the reported methodological details suggest a very poorly designed and conducted study. Some of the included papers do not even mention talcum powder products used with diaphragms. This systematic review is poor quality.

IARC (2006) ⁶²

Beginning in 1969 the International Agency for Research on Cancer (IARC) began a program to critically review the data on the carcinogenic risk of chemicals to humans. They subsequently expanded their reviews to include evaluation of carcinogenic risks associated with a range of exposures (including risks associated with biological and physical agents, lifestyle factors, complex mixtures of exposures, occupations, etc.) The purpose of the IARC program is to elaborate and publish detailed monographs including critical review of data, to evaluate human risks, and to indicate where uncertainty exists and where additional data are needed. They also give an overall assessment of the strength of the associations. It is worth noting that the individuals who contribute to IARC reports (the Working Group) include extremely knowledgeable and unbiased scientists who have specific content expertise and who have no apparent conflicts of interest. Invited specialists and representatives from international health agencies are brought in to supplement the scientific experts. In their evaluation, they heavily weight whether data support a conclusion of causality. They score evidenced into four categories, ranging from a) evidenced suggesting lack of carcinogenicity; b) inadequate evidence of carcinogenicity c) limited evidence of carcinogenicity and d) sufficient evidence of carcinogenicity. Category c is used when there is possibly carcinogenicity, and this category is not used lightly. An exposure meets category c if there is a positive association between observed exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance of bias or confounding could not be ruled out. They further categorize agents into 3 groups: Group 1, corresponding to d above (sufficient evidence), the agent is carcinogenic to humans; Group 2, which includes 2A (the agent is probably carcinogenic) and 2B: the agent is possibly carcinogenic to humans. A review focused on the risks associated with carbon black, titanium oxide and talc was published in 2006. The review included a detailed review of the individual studies examining perineal talc use as a risk factor for cancer. IARC concluded that perineal use of talc-based body powder is possibly carcinogenic to humans (Group 2B)

Huncharek (2003) ⁷²

This review of 16 studies assessed the relationship between genital exposure to talc and ovarian cancer using data for 5260 women with cancer and 6673 controls. The pooled OR for ever being exposed to perineal talc powder products was 1.33 (95% CI 1.16, 1.45). Small differences were observed in the estimated ORs by whether controls in the case-control studies were from hospital populations (OR 1.19, 95% CI 0.99, 1.4), or the general population (OR 1.38, 95% CI 1.25, 1.52). I believe these differences are small. In general, in case-control

studies, population controls are likely more relevant and valid. However, as with several of the other reviews, talcum powder exposure was assessed as any exposure rather than quantifying by intensity. No stratification by tumor subtype or invasiveness was performed.

Gross (1995) ⁷³

Gross reviewed 10 studies on the association between talc exposure and ovarian cancer using data on 1333 women with cancer and 2362 without cancer. To summarize the RR of malignant epithelial cancer types due to any exposure to talc, adjusting for ovarian cancer risk factors, the authors combined results from five studies for OR 1.29 (95% CI 1.02, 1.63). For an analysis of all cancers (borderline and invasive), they included data from seven studies for a similar OR of 1.31 (95% CI 1.08, 1.58). Notably, the authors did not provide any methodological details of how they identified, assessed, and combined studies, making the results difficult to fully interpret. As with several of the other reviews, they assessed any exposure to talc.

Harlow (1992) ⁷⁴

Harlow reviewed five previously published studies and summarized an OR, not adjusted for confounding factors, and added his own data for a crude estimated OR of 1.3 (95% CI 1.1, 1.6). Unfortunately, no methodological details were provided on how studies were identified, assessed, and combined or how exposure was defined, making the results difficult to fully interpret. Further, only the combined, estimated, non-adjusted crude OR was reported. Of note, the results of the five published studies used in the review (in contrast to the summary) are well described and of good methodological quality.

Systematic Reviews: Summary

The systematic reviews provide a remarkably consistent estimate of an approximately 30% increase in the risk of ovarian cancer associated with any talc powder products use. The studies summarized in the systematic reviews reported consistent results with little variability and closely overlapping estimates for ovarian cancer risk due to talc use. Further, the reviews suggest that the risks are greater for invasive serous cancer. I believe Penninkilampi provides a comprehensive and high quality review and his estimate is that women who regularly use talc powder products, defined as >3600 lifetime applications, have a 40% increased risk of ovarian cancer compared to women with no regular talc powder product use. The association was significant for serous cancers.

While the methodological approaches of these systematic reviews were generally valid, I believe they all shared the weakness of focusing on any talcum powder use rather than daily talcum powder use, and this motivated my own review (below).

Pooled Data

Two large studies pooled data from several studies. They are worth describing because of their larger sample size and strong methodology in comparison to the individual case-control studies.

Pooled Data 1: Terry (2013)⁶⁹

This report pooled data on ovarian cancer patients from a national research consortium and assessed the relationship between talc powder products exposure and ovarian cancer by histologic subtype and invasiveness. Data were from eight case-controlled studies and importantly included previously unpublished data. The authors tried to unify definitions across the studies, but the definitions nonetheless varied widely. The prevalence of genital powder use in the controls varied widely across participating study sites, ranging from 15%–45%, suggesting either large variations in the underlying populations or, probably more likely, variation in the definition of powder use that led to these differences.

The data were for a total of 8525 cases and 9859 controls in the primary analysis. The authors found that **genital talcum powder use was associated with an approximately 24% increased risk of epithelial ovarian cancer (OR 1.24, 95% CI 1.15, 1.33)**. When stratified by cancer type, the risk was increased for all cancers except mucinous cancer. Risks were approximately equally elevated for invasive and borderline tumors. They used a subset of patient data to determine RR of ovarian cancer for the highest talcum powder users, measured as cumulative lifetime perineal applications (defined as applications per month and months of the year). They also considered age (inclusion in the highest user group required more use at age 70 than age 40) and assessed risk of cancer among the highest users. **The odds of cancer in the highest talc exposure category was higher than for women who ever used talc (OR 1.37, 95% CI 1.19, 1.58)**. A significant dose response was seen when data on all patients were analyzed, with greater exposure leading to greater risk.

Pooled Data 2: Cramer (2016)⁷⁵

Cramer conducted several case-control studies on the relationship between genital talc powder use and ovarian cancer. He pooled data from a large number of these studies, described as reflecting study enrollment in 1992–1997, 1998–2002, and 2003–2008. This publication reports the analysis of pooled data from these separate enrollment phases and a more detailed characterization of those data. Cases were women who resided in Eastern Massachusetts and New Hampshire diagnosed with epithelial ovarian cancer between the ages of 18 and 80. Controls were women identified through random-digit dialing, driver's license lists and town resident lists. Women were interviewed in person, and details of talc use were elicited including the number of applications per month (allowing assessment of frequency of use), timing of use, and lifetime exposures. These descriptions gave far greater detail than most other reports and are thus an important contribution to the field. Further, more demographic and clinical history were obtained and described in these enrollments than for other reviewed studies. This report gave associations from pooled data for 2041 cases and 2100 controls. The larger size of the population, unified variables, and greater detail about cases and controls allowed a larger number of stratifications than other studies.

Overall, genital talc use was associated with an OR of 1.33 (95% CI 1.1.6, 1.52). An important observation was that risk decreased with time since last use. Thus, how often women regularly used talcum powder (daily, or weekly or monthly) was meaningful for predicting ovarian cancer risk, but not if the women had not used talcum powder for 5 or more years.

Women who reported using talcum powder daily (>30 applications per month) had an OR of 1.46 (95% CI 1.2, 1.78). Of note, among women in the ovarian cancer case group who used talcum powder, daily was the most commonly reported frequency of use. **When analysis used data on women who reported their total number of talcum powder applications, those in the highest group category (>7200 lifetime applications, the equivalent of 20 years of daily application) had an OR for ovarian cancer of 1.49 (95% CI 1.06, 2.1).**

Cramer conducted detailed analysis of factors that could influence/interact with the association between talcum powder and ovarian cancer. Some of the results are quite striking. First, a very strong interaction with race was noted. **African-American women seem to be at a particularly elevated risk of ovarian cancer following talcum powder exposure (OR 5.08, 95% CI 1.32, 19.6) compared with white women (OR 1.35, 95% CI 1.17, 1.55).** This finding calls for greater research given the higher incidence, and poorer outcomes among African American women. Asian women seem to be at reduced risk (OR 0.04, 95% CI 0.01, 0.34). **Analysis showed a strong relationship with menopausal status and use of hormone replacement therapy.** ORs were significantly increased in premenopausal women (OR 1.41, 95% CI 1.13, 1.75) and **postmenopausal women who used hormone treatment (OR 2.21, 95% CI 1.63, 3.0).** Postmenopausal women who did not use hormone therapy were not at increased risk of ovarian cancer (OR 1.0, 0.68, 1.49). **Interestingly, the risk of ovarian cancer among postmenopausal hormone-treatment users was elevated only if they used hormones before hysterectomy and tubal ligation but risk was substantial (OR 3.49, 95% CI 1.39, 8.75) if talcum powder was used before these surgeries (OR 5.85, 95% CI 2.89, 11.9) compared to talcum powder use both before and after surgery.**

These findings merit further assessment in other populations but raise the possibility that estrogen is important in ovarian carcinogenesis. The authors also stratified analyses by histologic type and found that the relationship between ovarian cancer and frequency of talcum powder use was significantly elevated for invasive and borderline serous cancer and invasive endometrioid cancer, but not for mucinous, clear cell or mucinous borderline cancer. **Among the most frequent users of talc the adjusted OR for invasive serous cancer is 1.54 (95% CI 1.15, 2.07).** This relationship was even stronger among premenopausal women (OR 1.85, 95% CI 1.21, 2.8) compared to postmenopausal women (OR 1.33, 95% CI 0.96, 1.85).

Pooled Data of Case-Control Studies: Summary

The increased risk of ovarian cancer associated with talc use was estimated at around 40% across these studies. The increased risk for serous cancer was even higher at 50%.

Case-Control Trials

A large number of case-control studies are published—too many to dedicate a paragraph to summarizing the methods of each.

21,24,36,40,74,76-99

I carefully read and abstracted data from each study. Without assessing the quality of the case-control studies, I included them in a table and sorted them by size of the reported effect

of talc on ovarian cancer risk. It's a way to get an overview of what they report – and Viewing them in this way is easy to see the general direction of the effect. All but two demonstrate a positive association ($OR > 1$) between any talc powder products use and ovarian cancer, with ORs ranging from 0.73–3.9 across studies, Table 5 .

Table 5: List of Case-Control Studies Sorted by Estimated Effect Size (Odds Ratio)

Year	First author			Odds ratio	Confidence interval
	2008	Goodman	367	602	0.99 (.70, 1.41)
1993	Tzonous	189	200	1.05	(.28, 3.98)
1989	Harlow	116	158	1.10	(0.70,2.1)
1999	Wong*	499	755	1.13	(0.89, 1.43)
2011	Rosenblatt	812	1313	1.13	(0.93,1.36)
1995	Purdie	824	860	1.27	(1.04, 1.54)
1989	Booth	235	451	1.30	(0.80,1.9)
1998	Green	824	855	1.30	(1.1, 1.6)
2008	Merritt	1576	1509	1.34	(1.06, 1.68)
2012	Lo-Cignaia	902	1802	1.34	(1.07,1.66)
2009	Moorman	1086	1057	1.37	(1.05, 1.80)
2008	Gates			1.41	(1.14, 1.76)
2012	Kurta	902	1802	1.41	(1.16, 1.69)
1988	Whittemore	188	539	1.45	(0.94, 2.22)
2015	Wu	1701	2391	1.46	(1.27,1.69)
2000	Ness	767	1367	1.50	(1.1, 2.0)
1997	Chang	367	564	1.51	(1.13,2.02)
1982	Cramer	215	215	1.58	(0.98, 2.47)
1997	Cook	313	422	1.60	(0.9, 2.9)
1999	Cramer	563	523	1.60	(1.18, 2.15)
1992	Rosenblatt	77	46	1.70	(.70, 3.9)
2016	Schildkraut	584	745	1.71	(1.26, 2.33)
2004	Mills	256	1122	1.74	(1.14, 2.64)
1992	Harlow	235	239	1.80	(1.1, 3.0)
1996	Shushan **	200	408	2.00	NA
2009	Wu	609	688	2.08	((1.34 3.23)
1998	Godard	170	170	2.49	(0.94,6.56)
1983	Hartge	135	171	2.50	(0.70, 10.0)
1992	Chen	112	224	3.90	(0.9,10.6)
2004	Pike			NA	

V. Rationale for and Explanation of the New Systematic Review

In previous systematic reviews that I have conducted, I have obtained the most meaningful and consistent results by narrowly defining the research topic of the review, including only studies that provide data on this narrow topic in a well-defined population and stratifying my analysis of the studies' results by relevant factors such as age or race/ethnicity. The benefit of this approach is more accurate, precise, and meaningful results, while the potential tradeoff is a reduction in general applicability of the results, because many studies may be excluded for inadequate data. I believe greater accuracy is more important because I want to be certain about the data I am describing. For example, when I conducted a systematic review on the use of transvaginal ultrasound as a diagnostic test for endometrial cancer, I initially stratified

the results by patient use of hormone therapy. The reviewed studies had consistent results, but only if profoundly different diagnostic criteria were applied for women who did and did not use hormone therapy. For this reason, I completed one review on hormone users and another on non-users. In this case, I had sufficient data to assess both groups.

In this review on talcum powder use, I had sufficient data to summarize results for regular users of talcum powder (as close to daily but reflecting use of talc powder products several times per week) and risks of serous cancer; I did not have sufficient data to summarize results for occasional users or risk of other cancer types. I believe the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer. I want to point out that this does not mean that other uses (i.e. less than approximate daily use) does not cause ovarian cancer, nor that talc powder products does not cause other types types of ovarian cancer (e.g. endometrioid cancer). Thus, for the systematic review below of case-control studies on the relationship between perineal exposure to talcum powder products and ovarian cancer, I focused on whether regular use of perineal (genital) talc increases the risk of the ovarian cancer. When possible, I focused on the most common and serious type, invasive serous ovarian cancer.

VI. New Systematic Review of Literature Quantifying Association Between Regular Frequent Genital (Perineal) Talcum Powder Products Application and Ovarian Epithelial Cancer Risk with A Focus on Invasive Serous Cancer.

Literature Search

I performed a literature search to identify primary research studies (not reviews) that included patient-level data on the association between talc and ovarian cancer. The literature search was performed in the Medline, Embase, and Scopus databases using keywords “ovarian cancer,” “talc,” “perineal powder” and “genital powder.” Abstracts of resulting publications were reviewed to identify if they addressed the topic and included data. Only English-language articles were reviewed. The references of identified articles and reviews were scanned to identify additional publications. Review articles, editorials, letters to the editor were excluded.

Article Selection

Articles were included based on relevance to the question: **Does the regular (as close to approximately daily) use of genital (perineal) talcum powder increase invasive epithelial ovarian cancer?** Because daily use was the most dominant use category, when studies stratified their results into quartiles of use, or lifetime applications, I included the highest use category that had a reasonable number of data points to reflect daily use. Wherever possible, data on invasive serous cancer were abstracted separately. When I found duplicate reports on the same patient group, the largest and most detailed publication was included. This usually meant the most recent publication, but not always. An important caveat is that I could not always identify duplicative results. I included data from the Terry 2013 pooled data study because it included new data from previous studies. I also included data from the Cramer

2016 pooled analysis and earlier publications with duplicative patients were not included. But I calculated the results both including and excluding these studies.

Exclusion

Studies were not included if they reported only crude ORs unadjusted for confounding factors. A few studies were excluded because, the research methods were poorly defined, even though they reported on women who frequently used talcum powder. Studies that asked participants a single question about ever use of talcum powder, without further quantification of exposure, were not included in the summary.

Defining Talcum Powder Products Use

Regular use was defined ideally as daily or at least more than 3 uses per week. I also accepted studies that defined use as “regular” where the description made it clear that this was regular use. Studies that reported “regular use” but defined it as use of less than this frequency, were not included. Regular use was selected to differentiate occasional use (which may include one-time or infrequent use or use during only a particular time of a woman’s menstrual cycle) from sustained regular use. Studies that asked participants a single question about ever use of talc, without further quantification of exposure, were not included in the summary. For example, Purdie reported that 52–57% of women reported ever using talc without further quantification and was not included. Several studies asked about *regular use* defined as at least once a month. These studies were not included unless they further characterized women into different categories of use; if so, I included data for women in the highest use category as long as this was group was large enough to be meaningful. When studies asked about ever use but defined use and stratified results by use, I included any data that may have reflected daily use. This measure of regular use is imprecise but is more accurate and meaningful than evaluating talcum powder exposure as any use.

Stratification of Analyses: Focus on a Single Histologic Type Where Possible

My review focused on invasive serous cancer where possible, but also included all invasive cancer. The decision to focus on a single histologic cancer type was in part because ovarian cancers include a broad range of types and association of talc and ovarian cancer might differ by type. I chose serous cancers because they are most common invasive ovarian cancer type. Importantly, serous ovarian cancer is the only histologic type for which most individual research studies accumulated sufficient cases for valid statistical analysis. This cancer type also has the least uncertainty in pathological diagnosis (see Section III, Histologic Types). Further and most importantly, serous ovarian cancer is the most aggressive histologic type, so identifying causal factors is important. Finally, I focused on invasive cancer (as opposed to borderline cancer) because the risk of death from invasive serous tumors is far higher than for noninvasive types, with growing consensus that borderline tumors may not be malignant.

Type of Exposures

Studies were included if they reported on perineal exposure (rather than exposure through sanitary napkins, diaphragms, or condoms) as this is the most common exposure type and is

likely to reflect the most consistent exposure. I did not exclude studies if they reported combined use, as long as the exposure included perineal use.

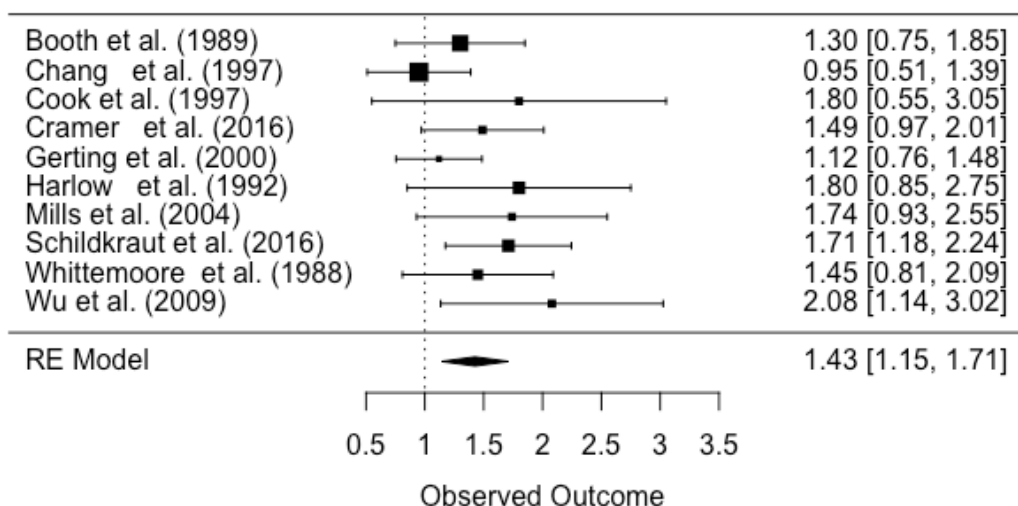
Statistical Analysis

Two individuals (Smith-Bindman and a consultant biostatistician) reviewed an abstracted data from each publication. Differences were resolved by consensus. The focus of the review was on quantifying the association between regular talcum powder products use and ovarian cancer, with a sub analysis on serous cancer and invasive cancer. Meta-analysis was performed using the metafor package in R (Version 3.5.1). The rma function was used to apply linear mixed effects models to study results and calculate summary statistics on effect size. Due to varying amounts and types of available data from each included publication, adjusted odds ratios (OR) and standard errors were used as the model inputs. Standard error (SE) was estimated using the relationship: 95% confidence interval = Effect size \pm 1.96*SE, assuming a roughly normal distribution of data and roughly symmetrical upper and lower confidence interval bounds. Incorporating adjusted ORs and SE into models in this way provides the added benefit of allowing model use of covariate-adjusted data (versus crude OR data). Weighting was done based on estimates of inverse variance. Study result heterogeneity was estimated based on maximum likelihood methods and was summarized via an I² statistic and associated p-value. The decision to include results from the cohort study by Gertig and colleagues (2000), which reported relative risk (RR), was based on the estimation that the RR value was only nominally different from the OR, a safe assumption in a study sample where less than 0.4% of the cohort developed the condition-of-interest.

Results

Overall 10 studies reported on daily talc powder products use and the risk of ovarian cancer. These studies were homogenous, and the odds of ovarian cancer associated with regular use was 1.43 (95% CI 1.15, 1.71). The included studies with associated point estimates are shown in a Forrest Plot in Figure 2

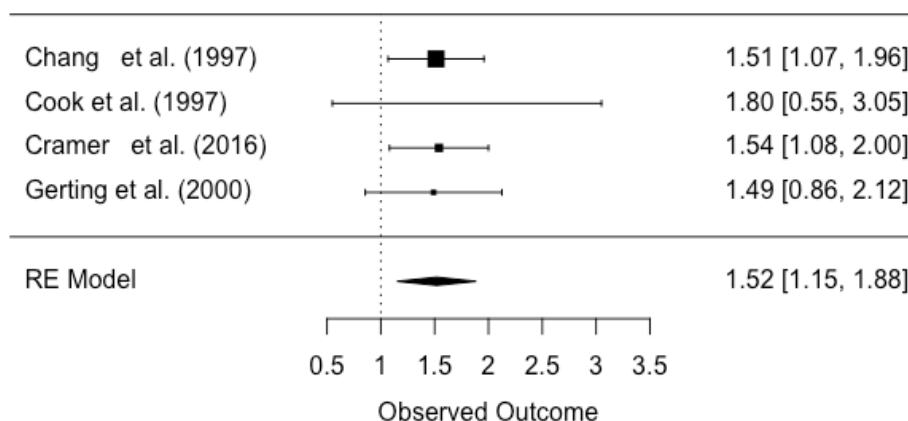
Figure 2. Forrest plot showing odds of ovarian cancer associated with regular use of talcum powder products.



The primary analysis of this excluded Terry, but the results were nearly identical if Terry was included

There were studies reported on regular talcum powder use and invasive serous cancer (or all invasive cancer if serous not reported) These studies were homogenous. The odds of invasive serous cancer associated with regular use was 1.52 (95% CI 1.15, 1.88). The results were similar when assessing the odds of all serous cancer.

Figure 3 Forrest plot showing odds of ovarian cancer associated with regular use of talcum powder products and invasive serous cancer.



New Systematic Meta-Analytic Review: Summary

The results of my systematic review of case-control studies on talcum powder use and ovarian cancer risk were consistent and indicate a **50% increase in risk of serous invasive cancer related to routine talcum powder exposure compared to no exposure**. This review had limitations including that study results were self-reported. I tried to be consistent in defining exposure, but this factor was subjectively determined by the individual studies. I tried to eliminate overlap of participant populations used in the included studies, but some patients may have contributed data to more than one study.

Overall Summary of the Epidemiology Data Describing the Association Between Talcum Powder Products and Serous Ovarian Cancer

I conclude, based on the review of the available primary studies, systematic reviews and my own quantitative review, that regular exposure to talcum powder products increases ovarian cancer risk by around 50%. The existing systematic reviews (in particular Penninkilampi and Berge) also concluded a significant increase in ovarian cancer risk following talcum powder exposure.

VII. Other Relevant Factors

Research Supporting Talcum Association with Ovarian Cancer: Transit to Ovary and Risk Reduction on Interruption

Evidence from relevant studies is clear that talcum powder particles applied to the genital region will ascend through the vagina and fallopian tubes and enter the pelvic cavity, reaching fallopian tubes and ovaries. In humans, this route has been established experimentally by labelling inert particles, applying them to the perineum just prior to planned hysterectomy, and then recovering them from the fallopian tubes following surgery. [Egli Fertil Stwriil 1961]

Further, talc particles have been found in normal and malignant ovarian tissue. Henderson found that in 10 of 13 tested epithelial ovarian cancer tumors, 75% had talc embedded in the tissue. This result confirms that talc reached to the areas with cancerous tissue, but not that it caused the cancer. Histological evaluation of ovaries removed because of ovarian cancer or benign conditions have identified both talc particles and asbestos fibers in the ovarian tissue, further supporting that particles applied to the perineum reach the ovaries.^{60,100} Heller found that in all women in a study who were having ovaries removed for benign ovarian growth had talc in their ovaries. These results confirm that talcum powder applied to the perineum may be absorbed into the vagina and migrate or be transported to the tubes and ovaries.¹⁰¹⁻¹⁰⁴ In 1967, Graham and Graham demonstrated that intraperitoneal application of asbestos in guinea pigs and rats results in overgrowth of ovarian epithelial cells comparable to the histologic changes in epithelial ovarian tumors in women. The greater frequency at which talc particles are discovered in ovarian cancerous tissue than in normal ovarian tissue further supports that these particles may be causing cancer.

Several epidemiological studies evaluated the risk of ovarian cancer associated with talcum powder products before and after women had tubal ligation or hysterectomy, which surgically removes the route by which talc reaches the ovaries. The studies strongly suggest that the increased risk of ovarian cancer associated with talcum powder products use is reduced or eliminated after tubal ligation or hysterectomy. The results support that the risk from talcum powder products is elevated when women have an open pathway from the perineum to the ovary that enables powder components to reach the ovaries via unobstructed fallopian tubes., The collective results demonstrate that talcum powder products are carcinogenic through direct transport/migration to the fallopian tubes and ovaries.

Variation in Risk when Talc Use is Discontinued

Several studies showed that the risk of ovarian cancer associated with talc powder products decreases as the time from discontinuation of powder use increases. For example, Cramer found an elevated risk of ovarian cancer with talc powder products use and the risk decreased as time since last use increased.⁷⁵

VIII. Consideration of Causality of Talc Powder Products and Ovarian Cancer : Bradford Hill Analysis

Causality is easiest to determine in studies such as randomized controlled trial, in which participants are randomized to receive or not receive a treatment, then their health is followed to see their response. However, people cannot ethically be randomized to be exposed to a potentially cancer-causing agent. Therefore, when assessing risk factors for cancer, the Bradford Hill Factors are often used. They provide a framework for assessing the weight of evidence to help decide if causality is likely, given a particular association, such as between talcum powder and ovarian cancer. The guidelines are imperfect and provide a framework as compared with an absolute set of criteria.

I address each of the Bradford Hill factors below, with my understanding of how the evidence of talcum powder products exposure supports or refutes causality. While the Bradford Hill Factors include nine aspects of association, they should not be used as a checklist for causation. Instead, they can help interpret associations and aid in inferring causality. For each factor, I have highlighted why I believe this factor is more or less important.

A) Strength of Association

It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, I do not believe this is necessarily the case. If a risk factor increases the risk of disease by 50%, and the exposure is common, it will have a far greater impact on a number of people, in comparison to a rare exposure that has a higher associated OR. And if the association is truly one that increases risk by 50%, then this is the magnitude of the association that will be detected. It is not intuitive that if an exposure increases a risk by 50%, this difference is not discoverable compared with an exposure that increases risk by 100%. A larger association between exposure and disease may be easier to identify, but I do not believe it is more likely to indicate causality or importance.

As an example, Table 6 shows an overview of the relationship between bladder cancer and two of its known risk factors; occupational industrial chemicals and smoking. Several industrial chemicals such as 2-naphthylamine are strongly associated with bladder cancer risk. In 1954, Case et al. reported a 200-fold increased bladder cancer risk for workers exposed to 2-naphthylamine. In cohort studies of rubber industry workers, elevated standardized mortality ratios (SMRs) as high as 253 (95% CI 93, 551) were reported. Use of some of these chemicals are now prohibited in Europe and their use is regulated in the United States because they cause cancer.(OSHA, 2011).

Cigarette smoking is also a known bladder cancer risk factor. However, the RR for smoking and bladder cancer is around 3, and therefore about 100 times lower than the RR for exposure to industrial chemicals. Yet bladder cancer is the second most common cancer attributed to smoking in the United States. It impacts a very large number of individuals. Of the 70,000 cases of bladder cancer diagnosed each year, as many as 60% are estimated as attributable to smoking.

Using the RR magnitude to quantify the “importance” of these two risk factors, industrial chemicals and smoking, would be misleading. Smoking will result in far more cancers than industrial chemicals, even though the RR is much lower. In the crude data in Table 6, of the approximately 70,000 bladder cancers diagnosed annually in the United States, 50,000 are thought to result from cigarettes while fewer than 1000 result from occupational exposures. A 50% reduction in smoking exposure will save 25,000 men from getting bladder cancer. Reducing industrial chemical exposures will saving around 500 men from getting bladder cancer. Thus, any impact on reducing known exposures for bladder cancer has the potential to be around 50 times more impactful if directed at smoking.

Table 6. An example showing the number of individuals who might be impacted through exposure to an occupational chemical that leads to bladder cancer as opposed to smoking.

	Occupational Exposure	
	2-naphthylamine	Smoking
Estimated odds ratio associated with exposure	200	3
Number of individuals exposed annually	10,000	50,000,000
Bladder cancers due to exposure annually	1000	50,000
Impact on number of cancers diagnosed annual if exposure reduced by 50%	500	25,000

The bladder cancer example highlights that a factor that increases risk by 50% will have an enormous impact on population mortality if the exposure is common or if the cancer is particularly lethal. This is certainly the case for talcum powder products, which are used by as many as half of all women in the U.S. Women’s use of talcum powder products is so widespread that even a relatively modest increase in risk would pose a sizeable health risk to the population. Further, a 50% risk increase is particularly important for ovarian cancer, which has a high mortality rate, with rare early detection.

Defining a “strong” association is critical for assessing potentially causal relationships. A current concept in epidemiology is that considerations about whether a factor causes a disease should weigh statistical validity and significance and the multiple factors that influence the disease. Thus, assessing *strength of association* when inferring causality requires examining underlying research and analytic methods, comparing the weight of evidence in the literature, and considering other contextual factors. The data supporting the causality of talcum powder products exposure for ovarian cancer is extremely strong.

Using the existing evidence, I reviewed and assembled for this report, I estimated how many ovarian cancers that occur each year in the United States are likely to be caused by exposure to talcum powder products in comparison to other risk factors for ovarian cancer, Table 7. This is a relatively simple analysis, but nonetheless is informative. The total number of ovarian cancers that are estimated to occur in the US annually is 22,240, and these will occur among

the 50.8 percent of the U.S. population of 311 million who are women. Of these ovarian cancer cases, approximately half (11,120) will reflect invasive serous carcinoma. For the purpose of this simple analysis, I have assumed that the elevation in ovarian cancer risk associated with talcum powder product exposures occurs only with invasive serous carcinoma. This is not true, but the data are the most certain for these cancer and this is a conservative assumption (meaning the true number of cancer and proportion of cancers caused by talcum powder product users will be even higher than my calculation). A proportion of ovarian cancers will occur among women who regularly use talcum powder products, and the remainder will occur in women who do not regularly use talcum powder products. If we estimate that women who use talcum powder products regularly have a 50% elevated risk of invasive serious cancer and we estimate the number of women who are exposed to daily talcum powder products is between 10% and 30% (this proportion is fewer than ever users of talcum powder products), then between 1,589 and 4,351 women will be diagnosed each year with invasive serous cancer caused by the exposures, reflecting between 14% and 39% of all invasive serous cancers and reflecting between 7% - 20% of all ovarian cancer diagnosed each year. This is a tremendous risk. This is a very large number of cancers to be caused by a product that provides no medical benefit. This Bradford Hill Factor of the Strength of the association is important and is met.

Table 7 An estimate of the number of ovarian cancers and invasive serous cancers caused by regular use of perineal talc powder products.

Proportion of women who regularly use Talcum powder products	Annual Invasive Serous Cancer in Women Exposed to Talcum Powder Products	Annual Invasive Serous Cancer in Women Not Exposed to Talcum Powder Products	% Invasive Serous Cancer in Women Exposed to Talcum Powder Products	% of all ovarian Cancer in Women Exposed to Talcum Powder Products
10%	1,589	9,531	0.14	0.07
20%	3,033	8,087	0.27	0.14
30%	4,351	6,769	0.39	0.20

B) Consistency of Associations in Different Populations and Studies

Another consideration for association and causality is consistency of the data. The data on the association between genital talc and ovarian cancer are highly consistent. The relative stability in the estimated increase in the risk of ovarian cancer associated with talc powder products use (50% increase for regular users of talcum powder and serous cancers; around 40% increase for all epithelial ovarian cancer and regular users of talcum powder products), as assessed across time and in diverse populations with diverse study designs, strongly argues that the causal association is real and satisfies the Bradford Hill guideline for consistency of associations across populations and studies.

C) Specificity Between Cause and Effect

The Bradford Hill factors suggest that associations are more likely to be causal when an exposure causes only one disease. While some examples of highly specific exposures and outcomes exist, many exposures and health concerns involve complex chemical mixtures and low-dose environmental and occupational exposures complicated by a variety of personal risk factors. A recent review stated, "The original criterion of *specificity* is widely considered weak or irrelevant from an epidemiologic standpoint."¹⁰⁵ Asbestos, for example, is associated with a range of cancers and various exposures. Regardless of doubts about the meaningfulness of this factor, talcum powder products are primarily associated with ovarian cancer and thus fulfills the specificity consideration, although this consideration is not one of the most important considerations for causality in my expert opinion.

D) Temporality

An exposure must come before an outcome for the exposure to be causal. Bradford Hill explained that for an exposure-disease relationship to be causal, exposure must precede the onset of disease. While this is self-evident, in epidemiological studies, reverse causality, in which behavior related to a health issue is influenced by knowledge or events about the issue, is always a concern. For example, women who undergo ovarian cancer treatment may begin using talcum powder products during their pre- and post-operative period because of symptoms or side effects perceived to be alleviated by talcum powder products use. Assessing talcum powder use without specifying the time of use might lead to women with ovarian cancer being more likely to report talcum powder products use. In this example, talcum powder may not have caused the cancer; rather, use of talcum powder products was caused by the cancer (and treatments). The importance of this issue led to Bradford Hill's consideration of temporality when assessing causality.

In essentially all of the case-control studies that assessed use of talcum powder products, women were specifically asked to report talc powder products only during past, not current periods; thus, the studies explicitly assessed exposure to talcum before cancer. Typically, questions were phrased "Did you ever use talc, but not in the last year before cancer diagnosis?" to exclude the year prior to diagnosis. This issue is not relevant for the included cohort studies, as women were surveyed about their exposures prior to cancer ascertainment. Thus, the temporality consideration is important for my consideration and is satisfied.

E) Dose Response

In general, when risks are proportional to exposure (e.g., doubling exposure doubles risk) this dose-response evidence is considered to support causality. Many of the reviewed studies did not collect sufficient data to carefully quantify the dose response, and many limited their comparisons to an ever/never comparison. This is in part what motivated me to complete my separate quantitative review to at least be able to dis-entangle ever into regular versus not regular use. The reviewed studies that did provide data that could be used to assess the

potential for dose response had mixed results in quantifying dose response. While most studies showed evidence of a dose response, others did not. For example, Schildkraut showed that >20 years of any genital powder use (OR 1.51, 95% CI 1.11, 2.06) showed a stronger association with ovarian cancer than <20 years of use (OR 1.33, 95% CI 0.95, 1.86).⁹⁹ Terry and Harlow showed significant dose responses, where ORs increased as exposures increased.^{69,74} The adjusted ORs increased from 1.3, to 1.5 to 1.8 with <1000, 1000–10,000, and >10,000 lifetime applications. Overall, any exposure to talcum powder resulted in an OR of 1.5; direct perineal application had an OR of 1.7 (95% CI 1.1, 2.7), daily exposure had an OR of 1.8 (95% CI 1.1, 3.0) and women with an intact genital tract who were estimated to have had more than 10,000 applications during ovulating years had the highest risk (OR 2.8 95% CI 1.4, 5.4). This exposure was found in 14% of women with ovarian cancer. Penninkilampi⁶⁷, the most comprehensive of the systematic reviews, also showed a dose response where women with more than 3600 lifetime applications had slightly higher risks as did women who reported long-term (>10 years) talc use. In contrast, Whittemore⁷⁷ showed no dose response, and Booth⁷⁸ demonstrated the reverse—the higher the dose, the lower the risks. The data from reviewed studies were too diverse to summarize a dose-response relationship. The measures of exposure frequency and duration varied, and the studies used different thresholds for quantifying exposures. Further, the measures to quantify dose tended to be crude, making the response even more difficult to establish.

In summary, most but not all studies of talcum powder products and ovarian cancer show a dose response, but the results are inconsistent, and more importantly, are not considered or assessed in most of the published studies. A dose-response relationship is not required for causality and in large part because data were not consistently available, this factor does not weight heavily in my consideration. Further, this factor did not weight heavily in my considerations in that not all exposures will have a dose response, and some will indeed have a threshold effect. This is important here because asbestos is believed to exhibit a threshold, rather than a linear, dose-response.

F) Biologic Plausibility: Factors Linking Talc and Ovarian Cancer

The epidemiological evidence suggests a strong and positive association between exposure to talcum powder products and invasive ovarian cancer. However, epidemiological evidence alone does not provide a mechanism or pathophysiological process that accounts for the increased risk. Nor does the epidemiological evidence confirm the specific component or ingredient in talc powder products that is responsible for carcinogenesis. Nonetheless, the data are persuasive that particles contained in talcum powder reach the tubes and ovaries, inflammation initiate a causal pathway, and that several components of talc powder products including asbestos, asbestiform fibers in talc, and heavy metals can contribute to the carcinogenicity of the products. This was a strong factor in my consideration of the evidence because there is extremely strong evidence that the components of talc powder products are known to be highly carcinogenic in other settings.

G) Coherence and Consistency with Understood Biology

The guideline of coherence is considered similar to biological plausibility. For both, the cause-and-effect explanation should be consistent with all knowledge available. For talcum powder and ovarian cancer, this consideration is easily satisfied.

H) Experimental Evidence

The evidence in humans of the impact of talcum powder products exposure and ovarian cancer development is based on a large number of observational studies. Direct experimental evidence in the form of randomized controlled trials in humans is simply not possible to generate, for ethical reasons. The experimental evidence in humans that talc particles can migrate to the ovary and be incorporated into ovarian tissue is relevant to developing a causal model but does not directly prove that that exposure causes cancer. There is also human data relating to the inflammatory nature of ovarian cancer. There is compelling in vitro research delineating the inflammatory mechanism by which talcum powder causes cancer. Animal studies showing inflammatory tissue effects and tumor formation with talcum powder exposure are also supportive.

I) Analogy

Bradford Hill implied that when evidence is strong of a causal relationship between a risk factor and disease, researchers should be more accepting of weaker evidence that a similar risk factor may cause a similar disease. Thus, analogy has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar. The strong evidence for the association between asbestos and lung cancer, and the chemical similarity between these minerals, as well as their fibrous nature, supports the analogy consideration and causal inference.

Summary: Consideration of Causality of Talc Powder Products and Ovarian Cancer using Bradford Hill

In consideration of Bradford Hill, the clear strength of the association (A), remarkable consistency in the published literature across a large number of populations and research studies (B), temporality (D) considered in all of the published studies, and perhaps most importantly, biological plausibility (F) were the criteria that I considered of paramount importance when assessing the causality of exposures of talc powder products and epithelial ovarian cancer

IX. Conclusion

In conclusion, substantial evidence supports a strong, positive and causal association between ovarian cancer and genital exposure to talcum powder products. Regular exposure to talcum powder products causes ovarian cancer in some women. This opinion is based on my extensive review of the medical and scientific literature, my own independent meta-analysis of the data, and my experience and expertise in the areas of epidemiology and women's health, including ovarian cancer.

All opinions are made to a reasonable degree of medical and scientific certainty. I reserve the right to amend or supplement this report as new information becomes available.

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63. Crowley. Expert Report of Michael Crowley, PhD, In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (Nov. 12, 2018). 2018.
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98. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2015;24(7):1094-1100.
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100. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *American journal of industrial medicine*. 1996;29(5):435-439.
101. Egli GE, Newton M. The Transport of Carbon Particles in the Human Female Reproductive Tract. *Fertility and sterility*. 1961;12(2):151-155.
102. Sjosten AC, Ellis H, Edelstam GA. Retrograde migration of glove powder in the human female genital tract. *Human reproduction (Oxford, England)*. 2004;19(4):991-995.
103. Venter PF, Iturralde M. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1979;55(23):917-919.
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105. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerging themes in epidemiology*. 2015;12:14.

Exhibit A

CURRICULUM VITAE
REBECCA SMITH-BINDMAN, MD

Title Professor, Radiology and Biomedical Imaging, Epidemiology and Biostatistics,
Obstetrics, Gynecology and Reproductive Sciences, Phillip R. Lee Institute for Health Policy
Director, Radiology Outcomes Research Lab, University of California San Francisco

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350 Parnassus Ave, Suite 307
San Francisco, CA 94117
Voice: 415 353-4946; Fax: 415 353-2790
Email: Rebecca.Smith-Bindman@ucsf.edu

EDUCATION

1980 - 1985	Princeton University	BSE	Engineering / Architecture
1985 - 1986	Columbia University		Post Bacc Pre-Med
1987 - 1991	University of California, San Francisco	MD	Medicine
1991 - 1992	University of California, San Francisco	Intern	Pathology
1992 - 1996	University of California, San Francisco	Resident	Radiology
1996 - 1997	University of California, San Francisco	Clinical Instructor	Radiology, Ultrasound
1996 - 1998	University of California, San Francisco	Fellow	Epidemiology & Biostatistics

LICENSES, CERTIFICATION

1992	California Medical License # G76462
1993	California X-ray Supervisor and Operator License RHL 143658
1996	Board Certification, American Board of Radiology

PRINCIPAL POSITIONS HELD

1998 - 2003	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Assistant Professor
2003 - 2009	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Associate Professor
2009 - current	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Professor
2014 - current	UCSF, Phillip R. Lee Institute for Health Policy Studies	Member
2000 - current	UCSF, Radiology Outcomes Research Lab	Director

OTHER POSITIONS HELD CONCURRENTLY

1999 - 2000	St Bartholomew's and The Royal London School of Medicine	Research Fellow
2009 - 2010	NIH, National Cancer Institute, Radiation Epidemiology Branch	Research Scientist

HONORS AND AWARDS

1985	Cum laude, Princeton University
1985	Senior Thesis Prize, Princeton University
1991	Student Summer Research Fellowship, Institute for Health Policy Studies, UCSF
1999, 2000	Nycomed Amersham Fellow, Radiologic Society of North America
2007	Nomination, Clinical Research Mentor of the Year, Bay Area Symposium on Clinical Research
2010	Nomination, CTSI Consultant of the Year, Impact Award
2010	Scientific Paper of the Year, Minnies, Auntminnie.com
2010	Finalist, Most Influential Radiology Researcher, Minnies, Auntminnie.com
2011	Leader in Imaging, Auntminnie.com
2012	Finalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2012	Semifinalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2012	Winner, UCSF Center for Health Care Value, Medical Center Initiative, Innovation Award
2013	Finalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2013	Runner-up, Scientific Paper of the Year, Auntminnie.com, Minnies
2013	Paper honored as 1 of the top 10 publications Funded by NCI's Epidemiology and Genomics Research Program
2014	Invited Editor, J of the American College of Radiology, March 2014, Radiation Dose Optimization
2014	Among Philip R. Lee Institute for Health Policy Studies faculty videos on UCTV, "Is Medical Imaging Harmful to Health: Opportunities to Influence Health Policy", most popular, N = 409,937
2015	Academy of Radiology Research, Distinguished Investigator Award
2015	Election to Fellowship, Society of Radiologists in Ultrasound

KEYWORDS AND AREAS OF INTEREST

Health Services Research, Outcomes Research, Disparities Research, Women's Imaging, Comparative Effectiveness Research, Quality Improvement, Dissemination and Implementation Sciences, Evidenced Based Radiology, Assessment of Population Impact of Screening Tests, Radiation Associated with Medical Imaging, Radiation as an Environmental Cause of Cancer, Management of Incidental Findings on Diagnostic Testing

OVERVIEW

Narrative

Dr. Smith-Bindman is a clinical researcher with expertise in health services research, epidemiology, outcomes research, comparative effectiveness research, and dissemination and implementation sciences focused on diagnostic imaging. Her research has focused on evaluating the quality, utilization, accuracy, predictive values and impact of diagnostic testing on patient health, and has quantified both the risks and benefits of medical imaging when used in different contexts and by different populations. One area of focus has been on evaluating racial and ethnic differences in access and utilization of screening mammography and how that contributes to higher breast cancer mortality among African American women, and on factors that influence the quality and access to screening among vulnerable populations (see references 33, 34, 37, 43, 46, 48, 61, 67 at the end of CV). A separate area of focus has been on quantified the variation in radiation dose associated with medical imaging across patients and institutions, and quantified the impact of radiation, particularly from computed tomography, as an environmental carcinogen. (see references 53, 58, 60, 62, 65, 68, 69, 72, 76, 78, 79., 81, 87, 89, 91, 97, 102, 107.) Separate from her research activities, she has been actively involved in translating evidence into changes in practice and policy. She has *informed policy leaders, practitioners and the public about* the safety concerns surrounding the use of radiation in imaging by describing the issue in main stream media, testifying before the US Congress, and by advising the FDA, The Joint Commission, the International Atomic Energy Agency, the International Council on Radiation Protection and leading professional societies. She has also written quality measures focused on radiation safety, and her work has resulted in organizations which monitor health care quality to adopt measures of diagnostic imaging safety.

Significant Publications

1. **Smith-Bindman** et al. Ultrasound vs Computed Tomography for Suspected Nephrolithiasis NEJM. 2014; 371:1100-10
2. Miglioretti DL, Johnson E, William SA, Grenlee RT, Weinmann S, Solberg LI, Feigelson HS, Roblin D, Flynn MJ, Vanneman N, **Smith-Bindman R**. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 167 (88): 700-7
3. **Smith-Bindman R**, et al. Risk of Thyroid Cancer based on Thyroid Ultrasound Imaging Characteristic: Result of A Population Based-Study. JAMA Internal Medicine. 2013 173(19):1788-96
4. **Smith-Bindman R**. Appendix F. Ionizing Radiation Exposure to the US Population, with a Focus on Radiation from Medical Imaging, included in Breast and the Environment: A Life Course Approach. The Institute of Medicine. March 20 2012
5. **Smith-Bindman R et al**. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. JAMA Internal Medicine 2009;169(22):2078-86
6. Curtis E, Quale C, Haggstrom D, **Smith-Bindman R**. Racial and Ethnic Differences in Breast Cancer Survival: How Much Is Explained By Screening, Tumor Severity, Biology, Treatment, and Co-morbidities. Cancer 2008 112(1):171
7. Goldman L, Haneuse S, Miglioretti D, Kerlikoswke K, Buist D, Yankaskas B, **Smith-Bindman R**, An assessment of the quality of mammography care at facilities treating medically vulnerable populations Medical Care 2008 46(7):701-8.
8. **Smith-Bindman et al**. Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med. 2006; 144(8):541-53
9. Haggstrom DA, Quale C, **Smith-Bindman R**. Differences in the Quality of Breast Cancer Care Among Vulnerable Populations. Cancer. 2005 Dec 1;104(11):2347-58.
10. **Smith-Bindman, R**, et al Endovaginal ultrasound to evaluate endometrial abnormalities. JAMA 1999;281:1693-4

PROFESSIONAL ACTIVITIES

CLINICAL

Attending physician, Ultrasound Section, Department of Radiology and Biomedical Imaging, UCSF, 25%. Includes supervised instruction of residents and fellows. My teaching focuses on how to use evidence to help inform interpretation of clinical examinations.

PROFESSIONAL ORGANIZATIONS

Memberships

1997 - 2018	Society of Radiologists in Ultrasound (SRU)
1997 - 2018	Radiology Alliance for Health Services Research in Radiology (RAHSR)
2013 - 2018	American College of Radiology (ACR)
2014 - 2018	American Roentgen Ray Society (ARRS)
2014 - 2018	Association of University Radiologists (AUR)

Service to Professional Organizations (selected)

2010 - 2011	American Board of Medical Specialties, American Board of Radiology, American College of Radiology, and Physician Consortium for Performance Improvements. Patient Radiation Dose Work Group
2011 - 2012	Institute of Medicine Committee on Breast Cancer and the Environment, commissioned report "Temporal Changes in Ionizing Radiation and Estimate of Contributions to Breast Cancer," contributing author
2012	Centers for Disease Control and Prevention, Cancer Prevention Work Group
2012 - 2014	The Joint Commission, Diagnostic Ionizing Radiation and Magnetic Resonance work group focused on issues of safety and guideline development
2012 - Present	International Council on Radiation Protection (ICRP) Task Group #79 on Defining Effective Dose Use in Medicine
2014	International Atomic Energy Agency (IAEA) United Nations General Assembly and Security Council. Special Committee Considering Population Impact of Low Dose Radiation
2015	Council of Distinguished Investigators of the Academy of Radiology Research

Service to Professional Publications (selected)

2000 - 2018	Journal of the American Medical Association (JAMA)
2000 - 2018	JAMA Internal Medicine
2000 - 2018	New England Journal of Medicine (NEJM)
2000 - 2018	Radiology
2000 - 2018	American Journal of Radiology
2000 - 2011	Journal of the National Cancer Institute
2000 - 2011	Health Affairs

2000 - 2015	Health Services Research
2000 - 2010	American Journal of Obstetrics & Gynecology
2000 - 2010	American Journal of Public Health
2000 - 2010	Annals of Internal Medicine
2000 - 2010	Journal of Medical Screening
2000 - 2010	Journal of Women's Health
2000 - 2010	Medical Care
2000 - 2010	Medical Decision Making
2000 - 2010	Obstetrics and Gynecology
2000 - 2010	Ultrasound in Obstetrics & Gynecology

INVITED PRESENTATIONS

International

2001	US - UK Cancer Learning Network, Deprivation and Cancer, <i>London, United Kingdom</i>
2001	British Society of Human Genetics, Prenatal Screening for Down syndrome in England and Wales and Birth Outcomes, <i>London, United Kingdom</i>
2002	Global Summit on Mammographic Screening, Europe Institute of Oncology, U.S.-U.K. Comparison of Screening Mammography, <i>Milan, Italy</i>
2005	University of Copenhagen, Does Practice Make Perfect; Association Between Volume and Accuracy of Mammography, <i>Copenhagen, Denmark</i>
2006	International Society for Prenatal Diagnosis, Prenatal Screening for Down syndrome in The Second Trimester of Pregnancy, <i>Kyoto, Japan</i>
2009	Canadian Breast Cancer Foundation, Forum on the Earlier Detection and Diagnosis of Breast Cancer, <i>Toronto, Canada</i>
2010	Nation Cancer Research Institute (NCRI), Risk of Cancer from Computed Tomography Examinations, <i>Liverpool, United Kingdom</i>
2013	Bach Mai University Hospital, Radiation for Medical Imaging: A Hidden Epidemic, <i>Hanoi, Vietnam</i>
2014	International Atomic Energy Agency (IAEA), Health Effects of Exposure to Low Dose Ionizing Radiation Associated with Medical Imaging, <i>Vienna, Austria</i>
2014	Korea College of Radiology, Tracking and Monitoring Radiation Dose and Its Impact Across the University of California Medical Centers and CT Radiation Doses Are Not What You Think: Why It's Important to Monitor and Track Dose Seoul, Republic of Korea
2016	International Atomic Energy Agency (IAEA), Exposure to low dose ionizing radiation from medical imaging and the health effects from these exposures. International Atomic Energy Agency. Technical Meeting on Science, Technology and Society Perspectives on Nuclear Science, Radiation and Human Health: The View from Asia, Singapore University
2016	University of North Carolina School of Medicine, Chapill Hill, NC, Radiology Department Grand Rounds , Diagnostic Imaging: Increasing Effectiveness and Safety Radiation From Medical Imaging,

- 2016 Singapore General Hospital, Singapore. Radiology Grand Rounds. Visualizing Patients and Their Dose to Improve Health Care Quality,
- 2016 St Luke's International Hospital, Tokyo, Japan. Hospital-wide grand rounds, Radiation from Medical imaging: A Hidden Epidemic.
- 2017 Childhood Leukemia International Consortium, Annual Meeting, Minneapolis, Minnesota, Estimating Radiation Exposure from Imaging Procedures
- 2017 Charity Hospital, Berlin, Germany. Radiology Grand Rounds, Radiation from Medical Imaging: A Hidden Epidemic
- 2017 Charity Hospital, Berlin, Germany, Imaging for Suspected Nephrolithiasis: Results from the Randomized Controlled Trial
- 2017 University Hospital, Basel, Switzerland, Radiology Grand Rounds. A Dose of Reality: The Need for Active CT Dose Management
- 2017 Center for Diagnostic Imaging Quality Institute Council of Medical Directors, Scottsdale, AZ Keynote: Radiation from Medical Imaging
- 2017 The Leap Frog Group Pediatric Computed Tomography Radiation Dose
- 2017 PCORI Advisory Panel on Communication and Dissemination Research Presentation UCSF CT Radiation Dose Registry to Ensure a Patient-Centered Approach for Imaging
- 2017 American Urological Association (AUA) Quality Improvement Summit, Baltimore Maryland Keynote Address. Imaging Wisely: Improving the Value of Medical Imaging
- 2018 Jakarta Radiology Society, Jakarta Indonesia. Dose Optimization Implementation to achieve better radiology service in Hospital Keynote Addresses: Radiation from Medical Imaging: A Hidden Epidemic and Optimizing Radiation Doses for CT
- 2018 Westmead Hospital Sydney Australia. Radiology Grand Rounds. Radiation from Medical Imaging: A Hidden Epidemic
- 2018 Westmead Childrens Hospital, Sydney Australia. Optiizing Radiation Doses For Pediatric CT
- National
- 2000 American College of Medical Genetics
- 2000 Society of Radiologists in Ultrasound
- 2000 Society for Health Services Research in Radiology
- 2001 Society of Radiologists in Ultrasound Annual Meeting

2001	Society for Health Services Research in Radiology
2002	Society of Radiologists in Ultrasound
2003	Breast Cancer Surveillance Consortium
2003	Society of Radiologists in Ultrasound
2003	Centers for Disease Control and Prevention
2003	RSNA 88th Scientific Assembly and Annual Meeting
2004	Institute of Medicine (IOM): Saving Women's Lives
2004	Breast Cancer Surveillance Consortium
2005	Improving Mammographic Quality Standards Institute of Medicine (IOM)
2006	Beth Israel Deaconess Medical Center, Grand Rounds
2006	National Institute Child Health and Human Development
2007	National Cancer Institute, National Institute of Health (x2)
2008	Mount Sinai Urban Health Institute; Metro Chicago Breast Cancer Taskforce, Partnerships in Translation: Advancing Research and Clinical Care
2008	University of Washington, Seattle, Washington, Grand Rounds, and Visiting Professor,
2008	HMO Research Network Conference (4 th annual), Danville, Pennsylvania
2009	Society of Radiologists in Ultrasound, National Conference on Management of Ovarian Cysts
2009	Canadian Forum for the Earlier Detection and Diagnosis of Breast Cancer
2010	Center for Disease Control & Prevention, Annual Cancer Registry Meeting, Atlanta, Georgia
2010	HMO Research Network conference, Emerging Frontier in Healthcare, Research Delivery, Austin, Texas
2010	National Council on Radiation Protection (NCRP), Communication of Radiation Benefits and Risks in Decision Making
2010	National Cancer Institute, Board of Scientific Advisors, Bethesda, Maryland
2010	American Statistical Association Conference on Radiation Health, Annapolis, Maryland
2010	Breast Cancer Surveillance Consortium Annual Meeting, Washington, D.C.
2010	Kaiser Permanente: National Radiology Leadership Group, held at the RSNA, Chicago, IL
2011	Cleveland Clinic, Health Care Quality Innovation, Cleveland, Ohio
2011	Auntminnie.com, Live WebEx Conference RADEXPO 2011
2011	University of New Mexico, Visiting Professor, External Reviewer, Resident Research Day
2011	Oregon Health Sciences University, Department of Emergency Medicine, Grand Rounds
2012	Society for Imaging Informatics for Medicine (SIIM), San Francisco, CA
2012	Brown University, Grand Rounds, Emergency Medicine, RI Hospital, Providence, RI
2012	Society for Imaging Informatics in Medicine (SIIM), Los Angeles, CA

2012 PharmMed OUT, Georgetown University, Washington, DC

2012 Agency for Healthcare Research and Quality, Rockville, MD

2012 Radiology Society of North America, expert witness in full day mock trial focused on radiation safety and whether radiologists need to communicate risks to patients, Chicago, IL

2012 University of Pennsylvania, Grand Rounds, Emergency Medicine, Philadelphia, PA

2013 Radiology Society of North America (RSNA), Controversies Session, CT Radiation and Risk: How Certain Are We of the Uncertainty? Chicago, IL

2013 American Cancer Society, Doc Talk Lecture Series

2013 Association of University Radiologists (AUR), Comparative Effectiveness and Patient-centered Outcomes Research, Los Angeles, CA

2014 Cancer.net Podcast, "CT Scans and Cancer Risk", Available Online at <http://www.cancer.net/blog/2014-10/ct-scans-and-cancer-risk>

2014 Oregon Chapter, American College of Emergency Physicians, Portland, Oregon

2015 Women in Government Foundation (non-profit, non-partisan organization of all U.S. female state legislators) Diagnostic Imaging. Increasing Its Effectiveness and Safety, at 16th Annual Southern & Eastern Regional Conference, Charleston S Carolina

2016 Lindeberger Cancer Center, University of North Carolina, Chappil Hill NC, Radiation From Medical Imaging: A Hidden Epidemic

2017 American Urological Association (AUA) Quality Improvement Summit, Baltimore Maryland Keynote Address. Imaging Wisely: Improving the Value of Medical Imaging

Regional Presentations (selected)

2000 Kaiser Permanente Department of Genetics, Oakland CA

2001 San Francisco State University, SF CA

2001 UCSF, San Francisco General Hospital, Department of Medicine, Grand Rounds

2001 American College of Obstetrics and Gynecology

2002 UCSF Breast Oncology Program Comprehensive Cancer Center Grand Rounds

2003 UCSF Obstetrics and Gynecology Grand Rounds, SF CA

2004 UCSF Multi-Department Symposium. Racial Disparity and Breast Cancer, SF CA

2004 UCSF Quality of Breast Cancer Care Symposium, SF CA

2005 Sisters Network, San Francisco (African American Advocacy Organization)

2005 Stanford University, Department of Health Research and Policy, Grand Rounds, Palo Alto CA

2006 UCSF, Lunch and Learn: San Francisco Community Outreach, SF CA

2006 Bay Area Health Care and Quality Outcomes, San Francisco, CA

2007 California Breast Cancer Research Symposium, Los Angeles, CA

2010 Bay Area Clinical Research Symposium, Plenary Speaker, San Francisco CA

2011	UCSF Department of Medicine Grand Rounds, San Francisco, CA
2011	San Francisco General Hospital Department of Medicine, Grand Rounds, San Francisco, CA
2011	UCSF, Department of Urology Grand Rounds, San Francisco, CA
2011	UCSF Department of Radiology Grand Rounds, San Francisco, CA
2011	Eden Hospital, Department of Medicine Grand Rounds, Alameda, CA
2011	Stanford Hospital, Department of Medicine, Grand Rounds, Palo Alto, CA
2011	Kaiser Permanente Medical Center, Multi-departmental Grand Rounds, San Francisco, CA
2011	UCSF Institute for Health Policy Studies, San Francisco, CA.
2012	Kaiser Permanente Medical Center, Grand Rounds, San Francisco, CA
2012	Kaiser Permanente Medical Center, Grand Rounds, Oakland, CA
2012	Massachusetts General Hospital, Department of Emergency Medicine, Grand Rounds Boston,
2012	Beth Israel Hospital, Department of Emergency Medicine Grand Rounds, Boston, MA
2012	Univ. of California Office of the President, Quality Improvement and Technology, Oakland, CA
2012	UCSF, Department of Radiation Oncology, Grand Rounds,
2012	Southern California Kaiser Radiology Chiefs Grand Rounds,
2014	UCSF, Endocrine Grand Rounds, San Francisco, CA
2015	California Society of Radiology Technologists, Annual Meeting, San Francisco, CA Keynote Address. Radiation from CT: A Hidden Epidemic. Strategies to minimize doses: What technologists can do?
2016	Society of Radiology in Ultrasound, Annual Meeting, Baltimore Maryland. Risk of Thyroid Cancer Based on Thyroid Ultrasound Imaging Characteristics
2016	UCSF, Breast Oncology Program, Radiation from Medical Imaging: A Hidden Epidemic and Approaches for Improving.
2016	UCSF Mini-Medical School Radiation Safety and Medical Imaging
2017	University of California Davis, Radiology Grand Rounds, Radiation from Medical Imaging; A Hidden Epidemic
2017	UCSF: Stand Up for Science: Panel Discussant

GOVERNMENT AND OTHER PROFESSIONAL SERVICE (selected)

2002 - 2003	CDC, National Breast and Cervical Cancer Early Detection Program, Planning Committee
2002 - 2005	Cochrane Collaboration Screening and Diagnostic Tests, Methods Working Group
2003 - 2003	Radiology National Boards, Examination Question Writer
2003 - 2010	National Cancer Institute, Physician Data Query (PDQ)

2004 - 2005	CDC, National Breast and Cervical Cancer Early Detection Program, Panelist, Committee on Assessment of Covered Benefits, Expert
2007 - 2010	California Health Benefits Review Program (CHBRP)
2008 - 2011	Center for Scientific Review, NIH, Health Services Organization and Delivery Study Section
2010 - 2011	American Board of Medical Specialties, American Board of Radiology, American College of Radiology, and Physician Consortium for Performance Improvements. Patient Radiation Dose Work Group
2010	Congressional Hearing, US House of Representatives, Energy and Commerce, Subcommittee on Health. Medical Radiation: An Overview of the Issues. Expert Witness
2010	Food and Drug Administration, Center for Devices & Radiological Health, National Meeting Focus on Radiation Safety, Presenter
2010 - 2011	National Quality Forum, Imaging Efficiently Steering Committee
2011 - 2012	Institute of Medicine Committee on Breast Cancer and the Environment, commissioned report "Temporal Changes in Ionizing Radiation and Estimate of Contributions to Breast Cancer," contributing author
2010 - 2011	Lung Cancer Screening with CT Evidence Review Committee. Multidisciplinary collaboration, including American Cancer Society, American College of Chest Physicians; American Society of Clinical Oncology & The National Comprehensive Cancer Network
2011 - 2016	International Council on Radiation Protection (ICRP), Task Group 79 on Defining Effective Dose Use in Medicine
2012	Congressional Hearing, US House of Representatives, Energy and Commerce, Subcommittee on Health, hearing on the Consistency, Accuracy, Responsibility, and Excellence in Medical Imaging and Radiation Therapy (The CARE Bill), Expert Witness
2012	Centers for Disease Control and Prevention, Cancer Prevention Work Group
2012 - 2014	The Joint Commission, Diagnostic Ionizing Radiation and Magnetic Resonance work group focused on issues of safety and guideline development
2013	Government Accountability Office: Medicare Imaging Accreditation Establishing Minimum National Standards and an Oversight Framework to Ensure Quality and Safety of Advanced Diagnostic Imaging Services, May 2013, Contributor
2014	International Atomic Energy Agency (IAEA) United Nations General Assembly and Security Council. Special Committee Considering Impact of Low Dose Radiation
2015	Council of Distinguished Investigators of the Academy of Radiology Research

UNIVERSITY AND PUBLIC SERVICE

Service Narrative

There are several activities to which Dr. Smith-Bindman has contributed. For seven years she participated in the NCI sponsored Physicians Data Query (PDQ), an NCI committee charged with presenting evidenced based, on-line, widely accessible and widely disseminated guidelines relating to cancer screening and diagnosis. She

participated in several activities related to breast cancer screening including acting as a reviewer for the CDC on assessing the guidelines for the National Breast and Cervical Cancer Detection Program, participating in coverage decisions, acting as reviewer and content expert for the CA Health Benefits Review Program analyzing several bills before the state legislature that would expand breast cancer screening to include MRI, and participating in the creation of several IOM Reports. She has participated in several community projects, such as acting on the board of an African American breast cancer advocacy group, and as a consultant to the Metropolitan Breast Cancer Task Force, charged with improving breast cancer mortality rates and racial disparities. During the last five years She has been very active in local, statewide and national efforts around improving radiation safety, including invited presentations to the FDA, testifying before the US Congress on two occasions, working with innumerable societies and government organizations on guidelines and submitting two endorsed quality measures on radiation safety to the National Quality Forum. Her involvement in service activities within the University have focused on increasing the quality and quantity of translational research through participation in several University-wide task forces. Dr. Smith-Bindman serves on several Medical Center Committees, focusing on improved oversight and stewardship around radiation, and projects to improve the efficiency and effectiveness with CT.

UNIVERSITY SERVICE (selected)

2001 - 2015	UCSF School of Medicine, Faculty Recruitment Committees, Radiology, Rad Onc, Medicine
2002	UCSF School of Medicine Dean's Leadership Retreat, Santa Cruz
2003	University of California, Blueprint for Regional Excellence in Breast Cancer Care
2003	UCSF School of Medicine Task Force, Future of UCSF and Mission Bay
2003	UCSF Medical Center, Hospital Exceptional Physician Award, Committee Co-Chair
2003 - 2004	UCSF School of Medicine Task Force, Physician Scientist Program Clinic-Based
2003 - 2005	UCSF School of Medicine Faculty Council
2005	UCSF School of Medicine, Dean's Leadership Retreat, Santa Cruz, CA
2005 - 2006	UCSF Department of Radiology Seminars and Presentation Committee
2005 - 2008	UCSF Department of Radiology Annual Research Symposium Abstract Review Committee
2005 - 2009	UCSF Department of Radiology, SEED Grant Review Committee
2006 - 2007	UCSF Pathways for Clinical and Translational Research
2008 - 2010	UCSF Pathways to Discovery, Clinical and Translational Research, Advisory Council
2007 - 2010	University of California, Office of the President, CA Health Benefits Review Program
2009 - 2017	UCSF, Radiation Safety Committee
2012 - 2014	UCSF Department of Radiology, Maintenance of Certification Committee
2012 - 2015	UCSF Medical Center, Center for Health Care Value
2013 - 2017	UCSF School of Medicine, Conflict of Interest Advisory Committee
2014 - 2016	UCSF Clinical Enterprise, Strategic Plan, Committee for Continuous Process Improvement
2015 - 2017	UCSF Clinical Enterprise, Utilization Management Committee

PUBLIC SERVICE

2003 – 2007	SF Sisters, an African American breast cancer advocacy group, board member
2008 - 2008	Metropolitan Chicago Breast Cancer Task Force, Chicago IL, unpaid consultant
2011 - 2014	National Quality Form, National Consensus Standard for Patient Safety. Measure Developer "UCSF CT Radiation Dose Patient Safety Measure" Measure endorsed
2015	National Quality Forum, Pediatric Measures. Measure Developer, "Pediatric Computed Tomography Radiation Dose" Measure endorsed

TEACHING AND MENTORING

Teaching Narrative

Dr. Smith-Bindman spends substantial time mentoring trainees in clinical research. The trainees have ranged in experience from high school students through mid-career UCSF faculty. The individuals have come from a broad range of departments at UCSF including Radiology, Internal Medicine, Hospital Medicine, Emergency Medicine, Obstetrics and Gynecology, and Urology, and have also come from the UCSF Medical School, The University of California Berkeley, and local SF high schools. On average, she meets with each trainee 1-2 hours per week while collaborating. An NIH Mid-Career Investigator Award (K24) supported her time mentoring these individuals.

She teaches in several formal classes in the department of Epidemiology and Biostatistics primarily targeted to post graduate students who are completing a master's degree in clinical research. She is actively engaged in teaching the Radiology residents and fellows while attending on the clinical service and provides frequent lectures to the Radiology residents focused at research methods; frequently teaches in courses organized by the UCSF Office of Continuing Medical Education for both radiology courses and courses within other medical specialties. The radiology courses focus on using evidence to interpret our studies (usually focused on ultrasound topics), the lectures for other medical specialties focused on how to use imaging more appropriately. As listed above, she also frequently gives grand rounds within UCSF, and nationally on using imaging more appropriately. Lastly, she organized and ran a large, ongoing, virtual symposium on Radiation Safety described below. Both the content and format of this meeting were novel.

TEACHING

Formal scheduled classes for UCSF students.

The first class listed is a course for UCSF Medical Students. The remaining are part of the coursework offered within the UCSF Masters in Clinical Research Program, Department of Epidemiology and Biostatistics

Year	Title	Role	Class Size
2002 - 2005	Epidemiology and Biostatistics, UCSF School of Med	Section Leader	20
2005	Introduction to Diagnostic Testing	Lecturer	18
2007 - 2008	Clinical Performance and Health Outcome Measurement	Lecturer	20
2011 - 2014	Translating Evidence into Policy: Theory and Design	Lecturer	30
2010 - 2015	Framing Research to Influence Policy	Lecturer	25

Post Graduate CME courses (1-5 lectures/meeting)

2001	UCSF Obstetrics and Gynecology Update, San Francisco, CA
2001	UCSF Primary Care Medicine, Aspen, CO
2001	Primary Care Medicine, Maui, HI
2001	Management of the Hospitalized Patient, San Francisco, CA
2001	Controversies in Women's Health, San Francisco, CA
2001	Diagnostic Imaging in Women's Health, San Francisco, CA
2001	MRI & Ultrasound Imaging, Lake Tahoe, CA
2002	Obstetrics and Gynecology Update, San Francisco, CA.
2002	17th Annual Primary Care Medicine: Concepts and Controversies, Aspen, CO
2002	10th Annual Controversies in Women's Health, San Francisco, CA
2002	Diagnostic Imaging in Women's Health, San Francisco, CA
2002	Diagnostic Imaging, Maui, HI
2002	Obstetrical, Gynecological and Abdominal Ultrasound, San Francisco, CA
2003	Primary Care Medicine, Diagnostic Imaging in Women's Health, Maui, HI
2003	11th Annual Controversies in Women's Health, San Francisco, CA
2003	Diagnostic Imaging for Disease Prevention, San Francisco, CA
2003	46th Annual Diagnostic Radiology Postgraduate Course, San Francisco, CA
2003	OB/GYN and Abdominal Ultrasound, San Francisco, CA
2003	MRI and Ultrasound by the Lake, Lake Tahoe, CA
2004	Women's Imaging, Sonoma, CA
2004	Primary Care Medicine, Maui, HI
2004	Diagnostic Imaging in Clinical Practice, San Francisco, CA
2005	Obstetrical and Gynecologic Sonography, San Francisco, CA
2005	Radiology Spring Training, Scottsdale, Arizona
2005	Abdominal Imaging, Montreal and Quebec, Canada
2006	Controversies in Women's Health, San Francisco, CA
2006	Controversies in Breast Cancer Screening and Diagnosis, San Francisco, CA
2006	Cutting Edge Radiology, Diagnosis and Intervention, Vancouver, Canada
2008	Primary Care Medicine: Update 2008, San Francisco, CA
2008	Diagnostic Imaging in Women's Health, San Francisco, CA
2008	Obstetrical/Gynecological and Abdominal Sonography, San Francisco, CA
2009	Primary Care Medicine: Update 2008, San Francisco, CA

2009	Obstetrical/Gynecological and Abdominal Sonography Update, San Francisco, CA
2011	Imaging of Kidney Stones, San Francisco, CA, Director
2011	Primary Care Medicine, Principles & Practice, San Francisco, CA, Keynote
2011	39th Annual Advances in Internal Department of Medicine, San Francisco, CA, Keynote
2011	Controversies in Women's Health, Department of Medicine, San Francisco, CA, Keynote
2012	Updates on Imaging, Maui, Hawaii
2013	UCSF Otolaryngology Annual Conference, San Francisco, CA
2017	UCSF Practical Body Imaging, Kona, Hawaii

Other Teaching

Radiation Safety and CT: Virtual Symposium. Innovative on-line Interactive CME course targeted to physicians (radiologists and those who order imaging), technologists, medical physicists, and trainees. This was created as an on-line, free, virtual meeting focuses on radiation safety. The initial creation of this virtual meeting began in 2013. Creating the meeting involved creating a multidisciplinary, on line, virtual meeting with over 100 lectures (see list of lectures, now offered freely on line - <http://rorl.ucsf.edu/speakers>), 10 live interactive sessions/chat rooms and over 500 registrants enrolled in the meeting during the “live days”, and ongoing attendees attend each month. The speakers at the meeting included numerous department chairs, the director of the Agency for Health Care Policy at the time, a US Congressman, leaders from numerous societies, The Joint Commission, The American Board of Internal Medicine Foundation, and innumerable scientific experts on diverse patient safety issues, and the meeting was an integration of diverse viewpoints and perspectives. Dr. Smith-Bindman directed this meeting and personally wrote and delivered 7 lectures for the meeting. The meeting was novel in format and content.

MENTORING

Pre-doctoral students directly supervised

Dates	Name	Program or School	Current Position
2004 - 2005	C. Kagay	UCSF Medical School	Radiologist, Private Practice
2005 - 2006	A. Ding	UCB/ UCSF MD/MPH	MGH
2005 - 2008	A. Venkatesan	UCSF Medical School	Resident, Stanford
2006 - 2007	E. Dinkelspiel	Urban High School	Student, Univ. of Chicago
2011 - 2015	J. Keegan	Lick Wilmerding High	San Luis Obispo College
2010 - 2015	P. Mehta	UC Berkeley/UCLA Med School	UCLA Medical School
2012 - 2013	J. Zhang	UC Berkeley	Senior
2014 summer	A. Fraser	University High	Georgetown College

Postdoctoral fellows and residents directly supervised

Dates	Name	Position	Current Position
1998 - 2000	M. Copanigro, MD	Radiology Resident / Fellow	Private Practice

1998 - 2000	N. Vincoff, MD	Radiology Resident / Fellow	Private Practice
2003 - 2004	E. Weiss, MD	OB GYN Resident	Private Practice
2003 - 2005	K. Schueler, MD	RORL Research Fellow	Private Practice
2003 - 2005	D. Haggstrom, MD	Internal Medicine Fellow	Indiana University, Faculty
2005 - 2006	K. Reid, MD	Internal Medicine Fellow	Emory Faculty
2005	A. Jensen	PhD student, Copenhagen	Faculty
2005 - 2006	B. Ching, MD	Radiology Fellow	Private Practice,
2005 - 2006	A. Cole, MD	Radiology Fellow	Private Practice
2005 - 2007	L. Goldman, MD	Internal Medicine Fellow	UCSF Faculty
2006 - 2010	J. Lipson, MD	Radiology T32 Scholar	Stanford Faculty
2007 - 2008	J Stengel, MD	Radiology Fellow	Private Practice
2007 - 2008	A. Heath, MD	RORL Research Fellow	Private Practice
2007 - 2009	R. Cho, MD	Radiology Fellow	Private Practice
2007 - 2009	D. Sellami, MD	Radiology Resident / Fellow	Private Practice
2008 - 2009	A. Kamath, MD	Radiology T32 Scholar	NYU Faculty
2009 - 2010	J Ching, MD	OB GYN Resident	Faculty
2009 - 2011	N, Brasic, MD	Radiology Fellow	UCSF Faculty
2010 - 2011	D. Sridhar, MD	Radiology Resident	Private Practice
2010 - 2012	P. Lebda, MD	Radiology Fellow	Cleveland Clinic Faculty
2010 - 2013	I. Burger, MD	Radiology Resident	Private Practice
2010 - 2013	G. Merry, MD	Radiology Resident	Private Practice
2011 - 2014	J. Mongan, MD PhD	Rad Resident / Fellow	UCSF, Faculty
2013 - 2014	S. Hou, MD	Radiology Resident	NYU Faculty
2013 - 2014	C. Lee, MD	Radiology Resident	UCSF Faculty
2013 - 2014	T. Morgan, MD	Radiology Resident	UCSF Faculty
2013 - 2015	LA Hampton, MD	Urology Resident / Fellow	Fellow, Wash U
2013 - 2015	V. Arasu, MD	Radiology Resident	Resident
2013 - 2015	N. Benedetti, MD	Radiology Resident	University of Wash Faculty
2014 - 2015	B Carpenter, MD	Radiology Fellow	UCSF Faculty
2014 - 2015	J. Hsu, MD	Radiology Fellow	Private Practice
2014 - 2018	J. Demb	Epidemiology	UCSF

Faculty Mentoring

Dates	Name	Department / Section	Current Position
2002 - 2005	John Shepherd, MD	Radiology / Musculoskeletal	UCSF, Faculty, Radiology
2004 - 2005	Elaina Curtis, MD	UCSF Visiting Fellow	Univer. of Auckland Faculty
2005 - 2006	John Stein, MD	Emergency Medicine	UCSF Faculty, Emerg Med
2005 - 2006	Max Wintermark, MD	Radiology / Neuro	UVA, Faculty, Radiology
2007 - 2013	Lauren Goldman, MD	Internal Medicine	UCSF, Faculty, Medicine
2008 - 2011	Larry Rand, MD	OBGYN / Maternal Medicine	UCSF, Faculty, OBGYN
2008 - 2014	Antonio Westphalen, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2009 - 2017	Liina Poder, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2010 - 2018	Ralph Wang, MD	Emergency Medicine	UCSF Faculty, Emerg Med
2014 - 2018	John Mongan, MD, PhD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2017	Cindy Lee, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2017	Tara Morgan, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2018	Maureen Kohi, MD	Radiology / Interventional	UCSF, Faculty, Radiology
2015 - 2018	Ben Franc, MD PhD	Radiology / Nuclear Medicine	UCSF, Faculty, Radiology
2017 - 2018	Brian Haas MD	Radiology	UCSF, Faculty, Radiology

RESEARCH AND CREATIVE ACTIVITIES

Research Narrative

Dr. Smith-Bindman's research focuses on understanding the impact of diagnostic testing on patient outcomes. She is the director of the UCSF Radiology Outcomes Research Laboratory, and her team includes several programmers, biostatisticians, a developer, and a handful of epidemiologists who serve as project managers for the funded grants below. Her research expertise is in areas of epidemiology, technology assessment, outcomes research, comparative effectiveness research, health services research, and dissemination and implementation sciences focused on imaging. The research has focused on evaluating the quality, utilization, accuracy, predictive values and impact of diagnostic testing on patient health, and has quantified both the risks and benefits of medical imaging when used in different contexts and by different populations. I am leading several studies that assess and standardize the radiation dose used for CT scanning, in order to minimize doses, without loss of diagnostic accuracy. Additional current research is focused on putting systems-based solutions in place to standardize the use of imaging. For example, ongoing projects focus on improving decision support provided to physicians to help improve the use of testing, using evidence to drive and guide the change in practice, and determining the optimal surveillance strategy for the follow up of incidental findings seen on CT imaging. The research projects she leads, listed below, are typically collaborative, involving researchers from diverse clinical areas and who offer diverse methodological expertise.

RESEARCH AWARDS

Current

PI	07/02/2014 - 06/30/2019
NIH	\$1,140,000 direct/yr1
CT DOSE Collaboration: Partnership for Dose	\$7,900,000 total

Collaboration across the US and Europe to standardize and optimize the doses used for CT. The study uses a novel randomized controlled trial design to compare simple feedback to a multicomponent intervention as strategies to optimize doses. There are approximately 125 hospitals participating in the trial.

PI	09/02/2013 - 08/31/2016
PCORI (Patient Centered Outcomes Research Institute)	\$492,163 direct/yr1
CT Radiation Dose Registry to Ensure a Patient Centered Approach for Imaging	\$2,069,365 total

Collaboration across the US and Europe to create benchmarks and standards for CT by pooling data from a large number of hospitals and outpatient facilities

PI	3/01/2015- 02/28/2020
NIH	\$1,834,410 direct/yr1
Risk of Cancer in Childhood Associated with Medical Imaging	\$10,600,000 total

Retrospective cohort across large integrated health care systems to assess imaging in pregnant women and children and to quantify the risk of childhood and adolescent cancer associated with these exposures.

PI (co-PI with Gould, Kaiser Foundation Research)	4/01/2015- 03/30/2020
PCORI	
Pragmatic Trial of More versus Less Intensive Strategies for Surveillance of Patients with Small Pulmonary Nodules	\$14,458,936 total

Prospective comparative effectiveness study across 15 health care systems to compare different strategies for the surveillance of lung nodules. The study is novel in that patients will be recruited with routine clinical care at imaging and the creation of systematic quality improvement strategies to ensure no loss to follow up.

Past

PI	10/01/2010 - 09/30/2013
AHRQ	\$4,830,368 direct/yr1
RCT of US versus CT for Patients with Suspected Renal Colic	\$9,210,000 total

15 Center randomized pragmatic comparative effectiveness trial comparing different strategies for imaging patients with suspected kidney stones. The study exceeded enrollment and follow up targets, and the primary results were published in the NEJM in 2014. Many additional analyses are ongoing using these data.

PI	09/01/2008 - 07/31/2015
NIH K24	\$172,000 direct/yr1
Mid-Career Development Award: Risk of Cancer Associated with Incidental Findings	\$868,632 total

PI	07/01/2011 - 07/01/2014
University of California Office of the President, CHQI	\$250,000 direct/yr1
Standardization and Optimization of CT Radiation Dose	\$750,000 total

Across the University of California Medical Centers.

Five-center observational study to collect radiation data across the five University of California campuses using automated techniques, analyze the sources of variation in dose, and conduct quality improvement initiatives to standardize practice

PI	09/30/2012 - 09/29/2014
CDC (Centers for Disease Control and Prevention)	\$250,000 direct/yr1
PEDS CT-DOSE: Pediatric CT Dose Optimization and Standardization Endeavor	\$500,000 total

Ten center observational study to collect radiation data and create benchmarks in children

Co-Investigator (PI Solberg, Health Partners)	07/01/2012 - 06/30/2014
PCORI (Patient Centered Outcomes Research Institute)	\$250,000 direct/yr1
Measuring Patient Outcome from High Tech Imaging Studies	\$500,000 total

Mixed methods study to understand imaging use, positive rates of imaging and patient perspectives on imaging, with respect to identifying patient centered outcomes important to patients.

PI	04/01/2009 - 03/31/2011
NIH / R21	\$317,000 total
Risk of Cancer with Incidental Findings Identified on US Imaging	

Retrospective cohort to understand cancer risks of incidental findings

PI	09/01/2008 - 08/31/2010
NIH / R21	\$317,000 total
Radiation Exposure from Imaging: are Doses in a Carcinogenic Range	

Retrospective cohort to understand use of medical imaging within integrated health care systems

PI	10/01/1999 - 07/01/2005
DOD	\$725,515 total
Outcomes of Screening Mammography in Elderly Women	

Medicare Data were analyzed to determine utilization of mammography and factors influencing survival

PI	09/01/1999 - 06/01/2005
NIH K07	\$635,687 total
Outcomes of Screening Mammography in Elderly Women	

NIH Career development award to study breast cancer screening among elderly women.

PI	07/01/2003 - 02/01/2007
California Breast Cancer Research Program	\$583,287 total
Racial Disparity in Breast Cancer Mortality	

Retrospective cohort to understand the causes for racial disparity in breast cancer outcomes

Co-Investigator (PI Kerlikowske UCSF) 04/01/2000 - 03/31/2005
NIH, U01 **\$3,100,000 total**
San Francisco Mammography Registry: A Research Resource

Dr. Smith-Bindman project lead on 1) Physician Predictors of Mammography Accuracy and 2) Validation of the Medicare Screening Algorithm

Co-Investigator (PI – McCune, UCSF) 09/30/2006 - 06/30/2011
NIH
Clinical and Translational Science Institute (CTSI)

The grant is to enhance training and infrastructure across UCSF. I participate in the Biomedical Informatics Program to educate trainees about imaging, epidemiology and study design

Co-Investigator (PI- Lu, UCSF) 04/01/2006 - 03/01/2009
NIH
Statistical Methods for Evaluation and Validation of Tests

Co-Investigator (PI Tlsty, UCSF)) 10/01/2005 - 09/30/2010
NIH
Biological Basis of Breast Density and Breast Cancer Risk

Co-Investigator (PI Esserman, UCSF) 05/01/2003 - 04/30/2007
Department of Defense/USAMRC **\$6,900,000 total**
Blueprint for Regional Excellence in Breast Cancer Care

PI 01/01/2002 - 12/01/2006
Women's Health Research Center, UCSF **\$70,000 total**
Down Syndrome Screening in the US

PI 04/01/2001 - 04/01/2003
Society of Radiologists in Ultrasound **\$40,000 total**
Prenatal Ultrasound for Detection of Birth Defects and Chromosome Abnormalities

PI 04/01/2001 - 04/01/2004
Society of Radiologists in Ultrasound **\$30,000 total**
Physician Variation in Ultrasound Accuracy

PI 07/01/2000 - 06/01/2001 **\$40,000 direct/yr**
Society of North America
U.S. U.K Comparison of The Accuracy of Screening Mammography

P
I 07/07/1999 - 06/01/2000
Radiologic Society of North America **\$35,000 direct**
Prenatal diagnostic ultrasound for the detection of chromosomal Abnormalities

MOST SIGNIFICANT RESEARCH PUBLICATIONS

- 1) **Smith-Bindman et al. Endovaginal ultrasound to evaluate endometrial abnormalities JAMA 1999**
Vaginal bleeding affects 7% of post-menopausal women, and historically women have undergone an invasive endometrial biopsy to exclude a diagnosis of cancer. This meta-analytic review found that endovaginal ultrasound is an easily tolerated non-invasive test that is accurate for the diagnosis of cancer, so that most women can avoid the need for an endometrial biopsy if they have a normal ultrasound test result. These results have been integrated into clinical practice guidelines in the US, Scotland, England, Germany, and Hong Kong. The publication has been cited 427 times based on SCOPUS accessed in 2015.
- 2) **Smith-Bindman et al. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA. 2001.**
Prenatal ultrasound is widely used to screen for Down syndrome, but the impact on patients has not been well studied. This meta-analytic review suggests that the use of ultrasound for the detection of fetuses affected by Down syndrome may be associated with more harm than benefit, as it can lead to large numbers of unnecessary amniocenteses and subsequent fetal losses with little evidence of benefits. This article was accompanied by extensive media coverage (AP, Reuters, NY Times), and controversy, and prompted discussion regarding the role of ultrasound in prenatal diagnoses. The manuscript has been cited 217 times based on SCOPUS accessed in 2015.
- 3) **Smith-Bindman R et al. US-UK Comparison of Screening Mammography. JAMA 2003.**
Screening mammography is an imprecise test, and there are considerable differences between physicians and programs in the accuracy of screening. This international comparison of screening mammography described 5.5 million mammograms obtained between 1996 to 1999 within three large-scale mammography registries or screening programs. Recall rates and open surgical biopsy rates were twice as high in the U.S. as in the U.K., although cancer rates were nearly identical. There was extensive media coverage (AP, Reuters, NY Times, Wall Street Journal, National Public Radio). These results have been widely cited, and were included in the IOM Report, "Saving Women's Lives." The publication was cited 223 times based on SCOPUS accessed in 2015.
- 4) **Smith-Bindman et al. Physician Predictors of Mammographic Accuracy. J Natl Cancer Inst 2005.**
Beyond the issues raised about the collective quality of mammographic screening in the United States, even more pronounced concern is the glaring variation among U.S. physicians in the ability to accurately interpretation their patients' mammograms. Dr. Smith-Bindman studied the accuracy of mammographic screening among 208 U.S. physicians, who collectively interpreted 1.2 million mammograms, and she found extraordinary variation in the interpretive abilities of radiologists; the sensitivity spanned 29% to 97%, while the false positive rate (the percentage of women who did not have cancer, but who underwent additional diagnostic testing or biopsy at their physician's recommendation) ranged from 1 to 29%. The difference in accuracy was principally due to differences in their training, experience and dedication to screening mammography; in short, the more experienced mammographers - and those who read more than the minimum number of mammograms required by MQSA guidelines - did substantially better. These findings have already been integrated into the Institute of Medicine's report on Mammography Quality Standards, regarding Enhancement of Interpretative Performance. The manuscript was cited 82 times based on SCOPUS accessed in 2015.
- 5) **Smith-Bindman et al. Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med, 2006**
Racial and ethnic minorities tend to have larger, more advanced stage breast cancers at diagnosis than white women, and African American women have significantly higher breast cancer mortality. It has not been clear, however, if this is due to inherent differences in biology or the utilization of screening mammography. This paper sought to disentangle whether biology or the use of screening was largely responsible for the known racial and ethnic differences in breast cancer. This study was

unique in that detailed cancer information was available from tumor registries that were linked with detailed information regarding mammography utilization. The results were striking. Most of the racial and ethnic differences in breast cancer features were reduced or eliminated after accounting for the frequency of mammography screening. The manuscript was cited 175 times on SCOPUS.

6) **Smith-Bindman et al. Second trimester prenatal ultrasound for the detection of pregnancies at increased risk of Down syndrome. Prenat Diagn 2007** *Prenatal ultrasound is widely used to screen for Down syndrome, but the impact on patients has not been well studied. Our meta-analytic review found that ultrasound was not useful and this prompted our large prospective study which evaluated ultrasound in a larger cohort, including nearly 20,000 women, in whom nearly 500 had fetuses affected by Down syndrome. This large study confirmed these preliminary results. The manuscript was cited 51 times on SCOPUS.*

7) **Smith-Bindman et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. JAMA Internal Medicine 2009** *This paper documented the variation in doses associated with routine CT. The widespread media attention that this paper received contributed to active policy discussion in this area. I was invited to present and discuss the results at the FDA, at a Congressional Hearing sponsored by the Health Subcommittee of the Committee on Energy and Commerce, and innumerable professional society meetings, and submitted (and had endorsed) a measure of quality around CT imaging by the National Quality Forum. The manuscript was cited 857 times based on SCOPUS accessed in 2015.*

8) **Smith-Bindman R, Appendix F. Ionizing Radiation Exposure to the US Population, with a Focus on Radiation from Medical Imaging, in Breast and the Environment: A Life Course Approach. The Institute of Medicine. 2012** *The IOM was commissioned to write a report on environmental causes of breast cancer. The Komen Foundation commissioned the report. I was asked to summarize what is known about the harmful effects of ionizing radiation on breast cancer risks. The IOM concluded that ionizing radiation is one of the largest, and the most preventable causes of breast cancer.*

9) **Miglioretti DL et al. Smith-Bindman senior author. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013** *Using a retrospective cohort design, this paper quantified the use of imaging among children within one of 7 large integrated health care systems, quantified the radiation exposure associated with these examinations, and estimated the likely impact of improved standardization of the conduct of CT on the risks of cancer. The manuscript concluded that if the top outlying radiation exposures could be reduced to the average (a modest goal) that 40% of expected cancer could be eliminated. The manuscript was cited 150 times based on SCOPUS accessed in 2015*

10) **Smith-Bindman R, et al. Risk of Thyroid Cancer based on Thyroid Ultrasound Imaging Characteristic: Result of A Population Based-Study. JAMA Internal Medicine. 2013.** *This retrospective observational study documented the risk of cancer associated with specific thyroid imaging findings. This is the first study that links a large cohort of patients with detailed imaging findings, with a comprehensive tumor registry to permit the quantification of the risk of cancer associated with specific findings. The results suggest that the number of biopsies can be reduced by up to 90%, with a relatively small impact on cancer detected. The results are being rapidly embraced by endocrinologists, surgeons and radiologists.*

11) **Smith-Bindman et al Ultrasound versus Computed Tomography for Suspected Nephrolithiasis NEJM. 2014.** *This 15-center randomized comparative effectiveness study assessed whether ultrasound or CT should be the first imaging test in patients with suspected kidney stones. The study is unique in using a rigorous randomized trial design to assess a diagnostic imaging test, and in assessing a broad range of outcomes other than diagnostic accuracy. Emergency department patients with abdominal pain and suspected nephrolithiasis*

were randomly assigned to one of three arms for imaging: ultrasound performed by an emergency medicine physician, ultrasound provided by a radiologist, or computerized tomography (CT). No significant differences were observed over the next 6 months in rates of severe serious adverse events (SAEs), related SAEs, or total SAEs, or ED or hospital admission rates at 7 or 30 days; however, initial imaging with ultrasound was associated with lower 1 day and 6-month cumulative radiation exposures than initial imaging with CT. The manuscript was cited 45 times based on SCOPUS accessed in 2015

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Current Exposure to Computed Tomography Imaging in US Integrated Health Care Systems, presented at the Conference on Radiation in Health by the Radiation Research Society, Kona, HI, 10/15-17, 2016

Current CT doses from a Computed Tomography Dose Registry in Pediatric Patients, Presented at the American Academy of Pediatrics Annual Meeting, San Francisco, CA, 10/22-25/2017

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Practical Strategies for Optimizing Dose, A Dose of Reality

European Congress of Radiology, European Society of Radiology, 2018
An International Randomized Controlled Trial of Two Interventions for Reducing Doses for Computed Tomography (CT) Through Audit Feedback and Sharing Best Practices

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Exhibit B

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Exhibit C

Rebecca Smith-Bindman Compensation and Prior Testimony

Dr. Smith-Bindman's fees are \$1,000/hr. She has not testified in other cases during the previous four years.

Exhibit 10

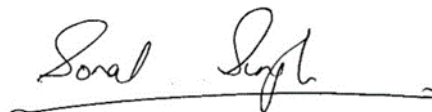
**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
SONAL SINGH, MD, MPH**

A handwritten signature in cursive script, reading "Sonal Singh", followed by a horizontal line extending to the right.

Date: November 16, 2018

Sonal Singh, MD, MPH

**TALCUM POWDER PRODUCTS AND RISK OF OVARIAN CANCER
EXPERT REPORT**

Prepared by

Sonal Singh, MD, MPH

University of Massachusetts School of Medicine

Nov 16, 2018

Table of Contents

I.	INTRODUCTION AND SUMMARY.....	3
II.	BACKGROUND AND QUALIFICATIONS.....	3
III.	PUBLICATIONS.....	5
IV.	STUDY DESIGN CONSIDERATIONS.....	7
V.	EPIDEMIOLOGY AND PATHOGENESIS OF OVARIAN CANCER.	14
VI.	WHAT CONSTITUTES COSMETIC TALCUM POWDER PRODUCTS?	14
VII.	SUMMARY OF OPINIONS.....	16
VIII.	METHODS FOR THE OVERVIEW OF SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES OF GENITAL TALC USE AND OVARIAN CANCER.	19
IX.	RESULTS.....	20
X.	BIOLOGICAL MECHANISMS OF TALCUM POWDER INDUCED OVARIAN CANCER.	57
XI.	ASSESSMENT OF CARCINOGENECITY OF TALC BY THE IARC IN 2006.	60
XII.	COSMETIC EXPERT REVIEW PANEL REPORT.....	61
XIII.	ASSESSMENT OF CAUSALITY.....	62
XIV.	CONCLUSIONS.....	66
	References	67
	Table 1. AMSTAR (Assessing the Methodologic Quality of Systematic Reviews) Rating of Systematic Reviews and/or Meta-analysis of Genital Talc use and Ovarian Cancer.....	77
	Additional Materials and Data Considered	79
	Other Materials	87

I. INTRODUCTION AND SUMMARY.

I have been retained to review scientific evidence and analyze the epidemiological data and, based on these data and other relevant evidence, to provide my professional opinion about whether talcum powder products are causally related to ovarian cancer. I have used a weight of evidence approach in examining the causal relationship between talcum powder products and ovarian cancer. I have relied upon my own systematic review of the literature and the cumulative body of evidence as the basis upon which I provide my opinions. This included gathering all relevant data based on *in vitro*, animal, and human epidemiologic studies on this topic. Although the weight of my opinions is derived from findings published in the peer-reviewed literature, relevant unpublished documents are also noted when applicable. The individual studies were examined for both reliability and validity noting their strengths and limitations. The cumulative body of evidence was then synthesized and examined and weighed using a widely accepted organizing framework- the Bradford Hill approach. (1). Using these materials, my education, and my prior clinical and research experiences, I have employed the methods generally accepted by the scientific community that would be used to develop a peer-reviewed manuscript.

In summary, it is my opinion, to a reasonable degree of scientific and medical certainty, that talcum powder products, specifically here Johnson's Baby Powder and Shower to Shower, can cause ovarian cancer. This finding is based on the totality of the medical and scientific evidence from meta-analysis, and consistent findings of a statistically significantly increased risk in observational studies, evidence of retrograde migration and inhalation of talc, presence of known or suspected carcinogens in Talcum Powder Products, and inflammatory tissue response that initiates multiple pathways and biological mechanisms by which talcum powder products can cause ovarian cancer. While these factors carry the most weight in my assessment, available data on the biological gradient of Talc exposure and ovarian cancer (dose response) also support my opinion.

II. BACKGROUND AND QUALIFICATIONS.

I am an Associate Professor in the Department of Family Medicine and Community Health and the Meyers Primary Care Institute, with a joint appointment in the Department of Quantitative Health Sciences at the University of Massachusetts Medical School, Massachusetts. I received

my M.B.B.S. (equivalent to M.D.) in 1998 from Patna Medical College, India. I then completed my internal medicine internship and residency in the Department of Medicine at the Unity Health Center, affiliated with the University of Rochester School of Medicine in 2005. Subsequently, I served on the Faculty as an Instructor of Medicine at Wake Forest University until 2007, and then as an Assistant Professor of Medicine in 2007. I received a joint appointment as an Assistant Professor of Epidemiology at Wake Forest University in 2008. While on the faculty at Wake Forest University, I obtained my master's in public health at Johns Hopkins University in 2008. I was an Assistant Professor in the School of Medicine at Johns Hopkins University as a recipient of the NIH Johns Hopkins Clinical Research Scholars Award in 2009. I held joint appointments in the Department of International Health and Health Policy and Managements and served as the Associate Director at the Center for Drug Safety and Effectiveness at Johns Hopkins University until 2016.

In my current position, I devote most of my professional time to epidemiologic research. I conduct clinical research with a focus on drug safety, evidence synthesis, and shared decision making. The major focus of my research is understanding the adverse effects of pharmacologic therapies. The remainder of my professional effort is dedicated to practicing general medicine and teaching activities. I have taught courses in systematic reviews, clinical epidemiology, pharmacoepidemiology, and the practice of internal medicine to medical students, interns, residents, and public health students at Johns Hopkins University and Wake Forest University. I have taught courses in clinical epidemiology and pharmacoepidemiology to researchers in the Bloomberg School of Public Health at Johns Hopkins University

I have served as an advisor to the World Bank, WHO International Agency for Research on Cancer and various pharmaceutical firms. I was part of World Health Organization International Agency for Research (WHO-IARC) panel which evaluated the carcinogenicity of various drugs and herbal products. (2). I currently serve as a member of the American College of Chest Physicians Guideline Panel. I have also been part of a panel that developed the PRISMA-HARMS (Preferred Item for Reporting Harm in Systematic Reviews and Meta-Analyses) checklist with an aim to improve the reporting of systematic reviews and meta-analysis of adverse effects. (3). My research has been funded by the Food and Drug Administration, the Agency for Health Care Research and Quality, the National Institute of Health and the Patient Centered Outcomes Research Institute. I am a recipient of numerous awards including the prestigious Johns Hopkins Clinical Research Scholars Award from the

National Institute of Health and the Tinsley R. Harrison Master Teachers Award at Wake Forest University School of Medicine. My systematic review on varenicline and the risk of cardiovascular events published in the prestigious Canadian Medical Association Journal was awarded the Best Research Paper of the year among hundreds of articles submitted to the Journal. I also serve as a peer reviewer for more than 50 journals and serve on the editorial board of prominent journals such as *BMJ Evidence Based Medicine*. I have reviewed grants for numerous federal and international organizations. I have conducted several epidemiological studies and systematic reviews and meta-analysis featured in prominent medical journals such as the *Journal of the American Medical Association* and the *British Medical Journal*. I have authored or co-authored more than 100 original peer-reviewed scientific articles and my work has been cited more than 13,000 times and my h-index is 48 [h number of papers which has been cited by others at least h times]. My work has been featured in *Science*, *Journal of the American Medical Association*, *British Medical Journal*, and the *Lancet*, as well as media outlets such as the *NYTIMES*, *Wall Street Journal* and *Washington Post*.

This background provides expertise in the use of epidemiological research methods in diverse settings, and in the clinical practice of medicine, both relevant to the present scenario. I have charged a rate of \$600.00 per hour in the preparation of this report. Attached as Exhibit A is a copy of my curriculum vitae.

III. PUBLICATIONS.

Below is a representative sampling of those articles published in leading medical journals such as *Journal of American Medical Association*, *Journal of American Medical Association-Internal Medicine*, and *British Medical Journal*. Please refer to my attached curriculum vitae for a complete listing of all publications.

- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone- A systematic review and meta-analysis. *Journal of the American Medical Association* 2007; 298: 1189-1195.
- Singh S, Loke YK. Furberg CD. Inhaled anticholinergics and the risk of major adverse cardiovascular events in Patients with Chronic Obstructive Pulmonary Disease: A systematic Review and Meta-analysis. *Journal of the American Medical Association* 2008; 300: 1439-1450. (CME Article in JAMA).

- Mills EJ, Wu P, Chong G, Ghement I, Singh S, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. *Q J Med* 2011; 104: 109-24.
- Singh S, Loke YK, Enright P, Furberg CD. Mortality Associated with Tiotropium Respimat® in Patients with Chronic Obstructive Pulmonary Disease- A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *British Medical Journal* 2011; 342: d3215.
- Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events with Varenicline: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Canadian Medical Association Journal* 2011; 183:1359-66. (with an editorial by JT Hays. Varenicline for smoking cessation. Is it a heart breaker?)- Best Research paper of the year award.
- Singh S, Loke YK. Drug Safety Assessment in Clinical Trials: Methodologic Challenges and Opportunities. *Trials* 2012, 13: 138.
- Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Ovarian cancer Mellitus: A Population-Based Matched Case-Control Study. *Journal of the American Medical Association Intern Med.* 2013 25:1-6.
- Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. Collaborators: Stewart BW, Biggar RJ, Lachenmeier DW, Singh S, Tsuda H, Baguley B, Marques MM, Tseng CH, Knight TL, Beland FA, Betz JM, Carcache de Blanco EJ, Cunningham ML, Dunnick JK, Guo L, Jameson CW, Karagas M, Lunn RM, McCormick DL, Witt KL, Zhou S. Carcinogenicity of some drugs and herbal products. *Lancet Oncol.* 2013; 14(9):807-8.
- Zorzela, L., Loke, Y.K., Ioannidis, J.P., Golder, S., Santaguida, P., Altman, D.G., Moher, D., Vohra, S., Boon, H., Clark, J., Derry, S., Gallivan, J., Gardiner, P., Gøtzsche, P., Loder, E., Napoli, M., Pilkington, K., Shekelle, P., Singh S, Witt, C., Lasserson, T., Wu, T., Shamseer, L., Mulrow, C. PRISMA harms checklist: improving harms reporting in systematic reviews. *British Medical Journal* 2016;352: i157.
- Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol.* 2016 Nov;4(11):943-956.
- Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular risks of exogenous testosterone among men. *Am J Med.* 2017 Dec;130(12):1449-1457.

IV. STUDY DESIGN CONSIDERATIONS.

I will examine the strengths and weaknesses of the study designs that are relevant to the present scenario. Each of the study-types discussed below has its advantages and disadvantages. Every study is subject to biases and error; none is appropriate and feasible for every situation. Instead, the evidentiary value of each study must be assessed and weighed on an individual basis, and in the context of the totality of the body of literature or scientific studies.

IV.I Randomized controlled trials. In double blind randomized controlled trials (RCTs) both the investigator and the participant are blinded to treatment assignment. All characteristics whether known or unknown, are evenly distributed at random between the intervention and placebo arm. Thus, if there are differences in incidence of outcome, it can be inferred to be a consequence of the exposure itself (i.e. causative).

However, the prospective nature of RCTs also results in several significant drawbacks for effects that are rare and/or slow to develop, like ovarian cancer. In addition to the ethical difficulties of administering a substance that may be harmful, such as talcum powder products, it is difficult prospectively to ensure study-subject compliance over the decade-plus timeframes required to assess ovarian cancer risk, and obviously impractical to have researchers administer a daily perineal talc application to study subjects. Similarly, there is no mechanism by which to randomly assign participants for non-modifiable exposures or the event may be sufficiently rare, such as in the present case of ovarian cancer to be evaluated in a randomized trial. The definitive randomized controlled trial in which patients would be randomized to talcum powder products and/or placebo and measure the outcome of ovarian cancer would be ideal. However, such a randomized trial does not exist, and such a randomized trial would be unethical.¹ Then again, randomized clinical trials are not necessary to establish causal evidence of harm. For instance, there is no randomized trial which supports the causal role of smoking in lung cancer. As a result, to address this question, we must rely on other study designs including observational studies and their meta-analysis to draw inferences on causation. The preponderance of evidence we have on harms of products are derived from such epidemiological studies.

¹ Defendants here have admitted this fact. Deposition of Linda Loretz 562:14-563:6 (October 1, 2018) (4); Deposition of Joshua Muscat 408:21-410:20 (September 25, 2018) (5).

IV.II Systematic reviews and Meta-analysis. A systematic review and meta-analysis is a study design wherein systematic searches are carried out to identify studies reporting on a question of interest. Systematic reviews provide a high level of evidence when evaluating the effect of interventions. (6).

The meta-analytic point estimate represents the sum of evidence from all the included studies. When individual studies may be underpowered to detect an effect, meta-analysis of cumulative studies may allow one to distinguish whether the entire body of evidence supports the presence or argues against evidence of a causal association. Apart from the P-value as a measure of statistical significance, the confidence intervals are used to assess the statistical variability around the estimate. In a meta-analysis the studies are weighted by the sample size of included studies with larger studies contributing more weight to the final estimate. Studies are examined to determine whether the findings are clinically and statistically homogenous or heterogenous. Clinical heterogeneity includes any differences in populations and interventions. It is also important to evaluate statistical heterogeneity among studies included in the meta-analysis. (7). Although some amount of variation in individual estimates of treatment effect is expected by chance, the excess of variation which cannot be explained by chance alone is referred to as statistical heterogeneity. I^2 is used as a measure of *statistical heterogeneity*—a percent of variation due to heterogeneity compared to chance, the higher the value the more the proportion of statistical heterogeneity.

The different approaches to modelling data across studies may yield slightly different results. Fixed effects meta-analysis which assumes that all the studies are measuring the same effect yield tighter confidence intervals, whereas random effects meta-analysis which assume that studies are measuring different effects in the population yield more conservative effects. Random-effects models may be more appropriate when the amount of statistical heterogeneity is high. Some amount of heterogeneity is expected when the database includes observational studies.

However, it must be noted that while meta-analysis can overcome issues of limited statistical power and provide information on consistency or inconsistency of effects, one needs to carefully examine the individual studies for their limitations and susceptibility to bias and confounding.

Thus, for example, if a study is too short to detect the effect in question, then even a patient-level pooled analysis of several such studies will very likely fail to detect a true causal relationship, even when one exists. This is an illustration of why it is important to consider study design, bias, and confounding in weighing the results from both individual studies and their meta-analysis. Systematic reviews are also susceptible to various publication and funding biases which need to be considered in interpreting results.

Meta-regression in using summary or group level published data may be susceptible to ecological or group level biases and result in spurious conclusions. (8). As a result, it is not recommended to evaluate the association between treatment effect, such as the difference in the risk of ovarian cancer, and participant characteristics at the study level (e.g., mean age of all participants) using aggregate level data, (9) as these may be susceptible to group level or ecological biases. An individual participant pooled analysis in which investigators have access to the patient-level data, such as that by Terry et al. discussed below, (10) is considered of higher quality than meta-analysis of summary data and provides the ability to reliably assess the effect of other patient and outcome related variables.

Umbrella reviews and overviews of systematic reviews. An umbrella review systematically collects and reviews evidence from multiple systematic reviews and meta-analysis and allows integration of evidence from multiple systematic reviews and meta-analysis, (11) to offer a much broader view of the evidence landscape. Individual systematic reviews and/or meta-analysis included in an umbrella review or overview should be critically appraised for quality. The 11-item critical appraisal tool AMSTAR (Assessing the Methodological Quality of Systematic Reviews) is a reliable and valid tool which provides an assessment of the quality of included systematic reviews and meta-analysis in an overview. (12).

What is the precise causal question or the hypothesis being tested? One cannot interpret the scientific evidence without being precise about the causal question that is being addressed when evaluating the association between any exposure and an outcome in any epidemiologic study. An exclusively narrowly framed hypothesis (e.g., evaluating only one route of exposure such as using talcum powder on contraceptive diaphragm), (13) while disregarding other important and relevant routes and mechanisms of exposure, is inherently limited by design. Since we may not have a complete picture of the underlying mechanisms or the timings of risk of products at the

time of study design, it is even more critical that studies on safety evaluate all potential routes of exposure.

IV.III. Cohort and Case-Control Studies. There are several considerations in interpreting data from prospective or retrospective observational studies or case-control studies. However, it is important to consider issues of study design, random error, systematic error, bias, and confounding in the interpretation of data. Random errors are statistical fluctuations in the measured data due to the limitations of the measurement instrument. They may occur in both direction because of the inability to measure exposure and outcomes in precisely the same manner. There is also the possibility of measurement error in the measurement of outcome and exposure in both study designs. If the measurement error is non-differential, such misclassification of exposure or outcomes usually biases findings towards the null. Systematic errors, by contrast, are reproducible inaccuracies that are consistently in the same direction, often due to a problem which persists throughout the entire study and are difficult to correct.

Case-control studies involve subjects diagnosed with the disease at issue, such as ovarian cancer (the “cases”), and a suitable number of subjects without the disease (the “controls”). Exposure is ascertained retrospectively among both cases and controls. The results are then analyzed to see if there is an association between the exposure and the disease. In contrast, prospective cohort studies are study designs in which subjects with and without the exposure of interest are recruited and followed up in time for the development of outcomes. This study design establishes temporality wherein the exposure precedes the outcome. It is important to determine the latency and induction between the exposure and the disease to assess the duration of follow-up. As an example, a 12-month follow-up study to evaluate the association between exposure to smoking and lung cancer would be unlikely to demonstrate an increase in the risk of lung cancer.

There are several strengths to the case-control design including the ability to ascertain long-term exposure-outcome relationships, particularly important to the present scenario because ovarian cancer develops over many years. Once cases and controls have been established, one can evaluate the association between multiple exposures and outcomes. In contrast, prospective cohort studies may be limited by the short-duration of follow-up which may be insufficient to ascertain the effect of exposure on long-term outcomes and bias their findings towards the null. Secondly, for relatively rare diseases, such as ovarian cancer, case-control studies are more

efficient. Because we are looking at the incidence of disease between the two arms of a study, a cohort study may have limited statistical power regardless of the actual number of subjects enrolled if the number of cases is small. For example, the Nurses' Health Study recruited almost 80,000 participants for only 307 cases of ovarian cancer. (14).

Both study designs are susceptible to selection bias when the selection of the participants into the study (or their likelihood of being retained in a cohort study) leads to a result that is different from the result had we enrolled the entire target population. In other words, the exposure-outcome relationship in controls or cases may be different from the target population. This can arise due to selection of controls not representative of the target population, non-response that is related to exposure and outcome, or differential loss to follow-up in a cohort study related to exposure and outcome status. Selection bias can bias findings either away from the null or towards the null.

Case-control studies, by their design, are generally not blinded and are also susceptible to bias as a result. They are also susceptible to recall bias, i.e. the concern that subjects with the disease may be more diligent in recollecting past uses. However, the degree of recall bias will depend on the type of exposure with chronic daily long-term exposures, such as talcum powder product use, being less likely to be subject to recall bias than intermittent short-term exposures. In contrast, prospective cohort studies in which subjects are recruited and then followed up for the development of outcomes are less susceptible to recall bias.

In addition, there is the issue of what may be called "behavior change" bias in cohort studies which may also bias their findings towards the null if exposure is only ascertained at baseline and not updated during follow up. This bias towards the null reduces the apparent effect of the exposure on the outcome. For example, if the subjects accurately report their talcum powder product use (or lack there-of) at baseline, but there is no follow-up, then the "ever" users' status will still be correct at the end of the study, because once having used talc, their "ever" status cannot change. This will not be true, however, of the "never" users; if they subsequently use talc, then without follow-up, their status will still be incorrectly recorded as "never." If there is a true causal connection, some ovarian cancers caused in the "never" category will, in fact, belong in the "ever" category, potentially biasing the study towards the null. Cohort studies are also susceptible to attrition bias and efforts should be used to minimize loss to follow-up. The main strengths of cohort studies are that if an effect (after adjusting for other confounding

factors) is found despite these biases towards the null, then it is more likely to be a causal relationship; the limitations being that they are less sensitive to determining a causal relationship. Case-control studies are based on past behavior and are not affected by this bias. Cohort studies are also susceptible to several prevalent user biases including potential bias due depletion of susceptibles. (15). A cohort study evaluating the association between talc use and ovarian cancer which limits the analysis to prevalent users (rather than new users), may largely be composed of survivors of the early effect of talc exposure on ovarian cancer, since new users who developed ovarian cancer after talc exposure may be ineligible for inclusion. This will potentially bias the estimates towards the null.

One important distinction to note is between risk factors for the disease and confounders. (16). A risk factor is an exposure which may explain the development or cause of disease in the population. These could be potentially modifiable or non-modifiable risk factors such as genetic risk factors. Confounding represents a special case of bias that results when the relationship between the risk factor -disease relationship is altered. A variable is considered a confounder only when ALL three criteria are present: a) the confounder is associated with the exposure in the population; b) the variable is related to the disease in the population; and c) the variable is not a link in the causal pathway to the disease. Risk factors that do not meet all the above criterion are not considered confounders of the exposure-outcome relationships (and thus may not require adjustment in the analysis).

Observational studies may also be susceptible to unmeasured confounding. Importantly, the potential for confounding does not mean that such a confounding exists. To address bias, confounders of the disease-outcome relationship need to be adjusted for in the analysis of epidemiologic studies. The methods for adjustment for known confounders include regression or propensity score methods. In establishing the effect of any exposure on an outcome it is important to disentangle the direct effect of an exposure of an outcome vs the indirect effect because of some mediators. The strength of association, in and of itself, does not denote whether a risk factor causes the disease. It is reflective of the background rate of the disease in the population and the relative risk of other competing risk factors. When the strength of association is weak, restricting the disease to a low risk population with low background rates of the diseases will magnify the association due to lack of competition among risk factors. (16)

One must be careful in interpreting data from subgroup analysis, such as analysis of various dose categories or age or ethnic groups, such as the case here with pre-menopausal women vs post-menopausal women or subgroup of women stratified by age, sex and ethnicity. The results of tests of interaction are important in interpreting data from such studies. If the test of interaction is not significant, this suggests that there is a lack of significant difference between the two groups. However, such subgroup tests can be underpowered because of reduction in sample size. Additionally, while a study may be internally valid it may not be generalizable to participants in the overall population beyond those included in the study. As an example, the cohort study of post-menopausal women reporting a non-significantly increased risk of ovarian cancer with genital talc use may not be generalizable to premenopausal women. (17). Despite the limitations noted above, most of our knowledge of the adverse effects of therapies has been derived from observational studies, since randomized controlled trials are not practical for several agents and rare outcomes.

It is also important to draw attention to the proper interpretation of P-values, confidence intervals and statistical significance. (18). I have followed the general principles laid out by the American Statistical Association on the interpretation of P-values and statistical significance. P-value can only indicate how incompatible data are with a statistical model. P-values do not indicate the probability that the studied hypothesis is true or the probability that data were produced by random chance alone. A P-value does not measure the size of an effect or the importance of a result and undue reliance should not be placed on whether a P-value passes a specific threshold. Full reporting and transparency are needed for interpretation of results. Confidence intervals (CI) measure statistical significance, (19) and indicate the precision and degree of uncertainty associated with a sample statistic. A 95% CI means that if we used the same sampling method to select different samples and computed an interval estimate for each sample, we would expect the true population parameter to fall within the interval estimates 95% of the time. CIs that remain elevated above 1 for relative risks (RRs) or odds ratios (ORs) are considered statistically significant. A narrow CI indicates a relatively higher level of precision. Non-overlapping CIs across two studies suggest a statistically significant difference between the study findings, whereas overlapping CIs may suggest consistent results. Thus, it is not necessary, and it is highly unlikely to have identical point estimates across studies to establish the presence of a consistent exposure-outcome association.

V. EPIDEMIOLOGY AND PATHOGENESIS OF OVARIAN CANCER.

Ovarian cancer is the most lethal gynecologic cancer in women. It is the leading cause of cancer death among gynecologic cancer in the US and the fifth most common cause of cancer with more than 14,000 deaths per year. The incidence is 11.4 cases per 100,000 women per year, with a mortality rate of 7.4 deaths per 100,000 women. (20). Approximately 1.3 percent of women will be diagnosed with ovarian cancer at some point during their lifetime. Approximately 22,400 new cases of ovarian cancer would be diagnosed in the US in 2017 with 14,080 deaths. (21).

Most women are diagnosed at an advanced stage of the disease and it is usually asymptomatic but may present as abdominal distention, bloating, and in a minority of cases vaginal bleeding. The prognosis is relatively poor when it presents at the advance stage where therapeutic options including chemotherapy offer little benefit. As discussed in more detail in Section X below, inflammation is known to play an important role in the pathogenesis of ovarian epithelial cancer through a mechanism of cell proliferation, oxidative stress DNA damage and gene mutations.

VI. WHAT CONSTITUTES COSMETIC TALCUM POWDER PRODUCTS?

- While I will examine the evidence of talcum powder products and their causal association with ovarian cancer, ascertaining what constitutes “talcum powder” it is important to emphasize that Talcum powder cosmetic products are not “pure talc.” The evidence I reviewed demonstrates talcum powder products contain asbestos, fibrous talc, heavy metals such as cobalt, chromium, nickel, and various fragrance chemicals (22)(23). This report evaluates the risk of ovarian cancer associated with talcum powder products and its constituents. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within.

- Talc is a naturally occurring mineral and its chemical composition is hydrous magnesium silicate with a chemical formula of $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$. In its natural form, talc may contain asbestos, also a naturally occurring silicate mineral, with a different crystal structure. Both talc and asbestos belong to the family of silicates that may occur in fibrous form, which is known to cause cancer. The structure of talc is characterized by a hexagonal sheet arrangement of silicon oxygen tetrahedral groups in a common plane. This results in a double-sheeted structure where the sheets are held together by weak van der Waals bonds. Talc consists mostly of these plate-

like structures ("platy talc") but talc can occur in fibrous form. Talc fibers are like asbestos fibers in size and shape. (22, 24).

- Despite claims that talcum powder products manufactured after the mid-1970s were "asbestos free," published articles, internal company documents, and testing of historical samples I reviewed demonstrate that talcum powder products can contain asbestos and other carcinogenic constituents as discussed below. For example, talc powders from national and international markets were analyzed by Paoletti et al. in a 1983 study to assess fiber content. (25). Samples of talc powders demonstrated fiber contents up to 30% of total particles. About half of the talc powders revealed the presence of asbestos. In some samples, a very high level of asbestos was revealed. (25). Consistently, the 1991 Blount study also found asbestos in cosmetic talcum powder. (26). In a recent deposition, the author of the 1991 study testified she had detected specifically in Johnsons and Johnsons baby powder. (27).

- Although the FDA conducted a survey of talc manufacturers in 2009-2010 and found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc, (28) the results were limited; only four out of nine talc suppliers submitted samples, and the number of products tested was low. The failure to detect asbestos could either be due to the technique used or the use of a non-representative sample. The FDA itself noted the study could not "prove that most or all talc or talc-containing cosmetic grade products currently marketed in the United States are likely to be free of asbestos contamination." (29).

- I reviewed Longo et al.'s report from August 2017 where he tested 30 bottles of Johnson's Baby Powder. (30). They found 17 samples contained detectable amounts of asbestos. They also found half of the samples contained fibrous talc. I also reviewed two additional reports from Dr. Longo where he found fibrous talc and asbestos in Johnson's Baby Powder. (31, 32). I reviewed the depositions and exhibits of Dr. John Hopkins, corporate representative for Johnson and Johnson, who testified to numerous positive tests for asbestos and fibrous talc. (33).

- In a recent report, Longo et al. (34) estimates that 37 out of 56 random samples (66%) of bottles of talcum powder products tested contain asbestos, which indicates that approximately 2 out of 3 bottles of talcum powder containing products are contaminated with asbestos. Talcum powder products are generally used by women habitually for months or years, rather than a

single application or a single bottle of use. Each successive use of a bottle of talcum powder product by an individual further accentuates the cumulative probability of their exposure to asbestos, beyond the probability conferred by the use of a single bottle. I reserve the right to supplement my report in order to estimate this probability of exposure to asbestos through habitual use of talcum powder products contaminated with asbestos, once the analysis of additional samples of talc is complete. Longo et al. also estimates that 41 of 42 random samples of bottles of talcum powder products tested contain fibrous talc. I reserve the right to supplement my report in order to estimate this probability of exposure to fibrous talc through habitual use of talcum powder products contaminated with fibrous talc, once the analysis of additional samples of talc is complete.

- I also reviewed the deposition and exhibits of Julie Pier, corporate representative for Imerys Talc America, Inc., who testified to numerous positive tests for asbestos and heavy metals between 1985 and 2002. (35).
- My review of monographs published by the International Agency for Research on Cancer (IARC) show that asbestos is a well-established carcinogen and unequivocally known to cause several cancers including mesothelioma of the lung, larynx, and ovarian cancer. (36). Overall, the International Agency for Research on Cancer Working Group classified asbestos compounds as “carcinogenic to humans” (Group 1) in 2012. (36, 37). IARC has also concluded that talc including asbestiform fibers grown in an asbestiform habit - commonly termed “fibrous talc” - is “carcinogenic to humans” (Group 1). (38).
- I also reviewed documents demonstrating talcum powder products may contain heavy metals such as chromium, nickel, and cobalt. (22). Asbestos, chromium, and nickel were all classified as a Group 1 carcinogens by IARC. (36) Cobalt is also present in talcum powder products and classified by IARC as a Group 2B carcinogen.

VII. SUMMARY OF OPINIONS.

1. **Statistical Significance.** There is a statistically significant increased risk of ovarian cancer with talcum powder products as demonstrated by most meta-analyses to date. (10, 39-42). Although a flawed analysis conducted limited to the use of talc dusted diaphragms and ovarian cancer conducted on behalf of the manufacturer reported an excess risk which was not

statistically significant, (13) it had several data extraction errors and was of lower methodological quality. (43). Several independent meta-analysis by academic researchers, some of which include individual participant data, (10) and the most recent meta-analysis reported a statistically significantly increased risk of ovarian cancer associated with perineal talc use, (42) rendering the previous findings of Huncharek et al obsolete. The studies of the highest rated methodologic quality as shown in **Table 1** which provides a methodologic grading of the quality of the included systematic reviews using the AMSTAR checklist have reported a statistically significantly increased risk of ovarian cancer associated with genital talc use. (10, 41, 42). See Section IX.IV for a summary of findings from epidemiological studies.

2. **Consistency and Replication.** These findings of a statistically significantly increased risk of ovarian cancer with talc use have been consistently replicated by several independent investigators in different population, and different settings across different data sources using different study designs. These slight differences in magnitude of risk reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time. The meta-analysis of case-control studies has consistently shown a statistically significantly increased risk, whereas the meta-analysis of cohort studies has also shown an excess risk, (42) which failed to reach statistical significance, due to inadequate statistical power and low number of events; but the confidence intervals of results between the two study designs overlap providing evidence of consistency. The number of ovarian cancers in the case-control studies exceeds the number of ovarian cancers in the cohort studies by several fold. (42).

3. **Strength of Association.** The cumulative strength of association for the increased risk of ovarian cancer associated with talcum powder containing products is significant and ranges from 30 % to 60% %. The strength of association is similar to estimates of other established carcinogens (e.g., 24 % increased risk of lung cancers in non-smokers exposed to environmental tobacco smoke) (44), hormone replacement therapy and breast cancer (RR 1.33, 95% CI: 1.24-1.44) (45), particulate matter and lung cancer (PM_{2.5}: RR 1.09, 95% CI: 1.04, 1.14 and PM₁₀: 1.08, 95% CI: 1.00-1.17). (46). Beyond carcinogens, there are well established examples of causal associations in epidemiology, such as in the case of particulate matter and myocardial infarction, where the statistically significant excess risks are in the order of even less than a percent (carbon monoxide: 1.048, 95% CI: 1.026-1.070; nitrogen dioxide: 1.011, 95% CI, 1.006-1.016; sulfur dioxide: 1.010, 95% CI: 1.003-1.017; PM₁₀: 1.006, 95% CI: 1.002-1.009; and PM_{2.5}: 1.025, 95% CI: 1.015-1.036 and ozone: RR 1.003, 95% CI: 0.997-1.010; P = .36). (47).

4. **Exposure-Response Assessment.** The assessment of exposure-response or biological gradient is hindered by the difficulty in quantifying talcum powder use usually collected by

self-reported data (frequency, amount, and duration), timing and patterns of use (e.g., douching), and other individual factors (e.g., co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. As discussed in the dose-response summary of epidemiological studies below, some studies have measured the frequency of exposure, others the duration of exposure with few studies measuring the combined duration and frequency or intensity of exposure. (48). It is important to interpret the exposure-response data in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer through alteration of the redox state in epithelial ovarian cancer cells, (49) and a monotonic dose-response curve may not accurately reflect this mechanism of development of ovarian cancer mediated via inflammation and alterations in redox states. Some epidemiologists have argued that it is difficult to know how dose-response should be modelled and it is unclear why nature would mandate a monotonic dose-response gradient. (50). Although it is difficult to know how to model the talc-ovarian cancer exposure-response assessment, it is possible that an agent which accelerates the development of cancer could account for threshold effects rather than monotonic dose-response effect. Despite these challenges, I address studies which have shown evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 57). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis reported an increased risk with >3600 lifetime applications compared to <3600 lifetime applications of perineal talc based on data from case-control studies. (42). A limited number of studies have shown no evidence of dose-response either with increased frequency or duration of exposure. (58-60).

5. **Retrograde Migration of Talc and Routes of Talc Exposure.** Talcum powder particles can migrate to the fallopian tubes and ovaries. (61-63). Talc and/or other constituents have been detected within the ovaries of women who report perineal talc use, (64) and found deeply embedded within ovarian tumors. (62, 65). Talc has also been reported in the lymph nodes which could occur through migration absorption or inhalation with transport through the lymphatic system. (66). Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of “measurable quantities of talc” in unrelated monkey models, (67) the timing and techniques of assessment and intraspecies differences could not completely rule out migration of talc particles. Furthermore, supportive evidence for migration comes from the findings of a decreased risk of ovarian cancer with tubal

ligation and hysterectomy, (62) evidence of migration of other particles such as starch. (68). The FDA concluded that the “potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable.” (69). A secondary route of exposure is inhalation. (36, 70).

6. **Multiple Biological Mechanisms of Talc Induced Ovarian Cancer.** Although not an absolute requirement for demonstrating causality, there is strong evidence that talcum powder products can induce ovarian cancer through established biological mechanisms (Section X). (39, 49, 71, 72). Inflammation plays a leading role in ovarian cancer and talc has pro-inflammatory effects; it also induces alterations in redox potential and pro-oxidant effects. (49) In ovarian cells talc has been shown to increase proliferation, increase neoplastic transformation and increase reactive oxygen species in the ovarian cells. (71). Talc has also been shown to be mutagenic in human ovarian epithelial cells through increased activation of gene activating transcription factors. Finally, the presence of asbestos and other Group 1 carcinogens likely contributes to the carcinogenicity of talcum powder products, and provides biologic plausibility for the consistent and significant increased risk seen in the epidemiologic studies on Talc and Ovarian cancer.

VIII. METHODS FOR THE OVERVIEW OF SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES OF GENITAL TALC USE AND OVARIAN CANCER.

I conducted an overview of systematic reviews and meta-analysis of observational studies of genital talc use and ovarian cancer. I included systematic reviews regardless of the performance of quantitative synthesis as meta-analysis may occasionally not be performed for data from observational studies. To inform the causal question, I also evaluated additional studies which provided evidence on the causal question of whether talcum powder products induce ovarian cancer. I critically appraised the meta-analysis using the 11- item AMSTAR (Assessing the methodologic quality of Systematic Review) checklist for systematic reviews and meta-analysis. (12) The individual epidemiological studies were also evaluated and summarized for their key strengths and limitations.

VIII.I. Systematic search. I performed an initial systematic search of Scopus and PubMed with the following search terms on June 12, 2017:

Pubmed: ("talc"[MeSH Terms] OR "talc"[All Fields]) AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All

Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields]
AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])

Scopus: (TITLE-ABS-KEY (talc) AND TITLE-ABS-KEY (ovarian AND cancer)

VIII.II Eligibility Criteria. I included and considered epidemiological studies, including case-control studies, cohort studies and systematic review and meta-analysis which reported on the association between talc and ovarian cancer. I searched the references of included studies and citing articles to find additional original articles. I also included in vitro, animal, and human epidemiologic studies that reported data that either support or refute the role of talc in the development of ovarian cancer. I excluded duplicate articles identified in the two databases, articles with no original data, narrative reviews, commentaries and opinion pieces, and citations not relevant to the present scenario. The title and abstracts of each manuscript were reviewed to identify potential studies for inclusion in this report. I also searched the reference of included studies to find relevant citing articles. New studies were identified after evaluating citing articles. I reviewed the full length of each of these manuscripts and provide a summary of their key findings below.

IX. RESULTS.

The results of the initial search yielded 273 citations. I included 9 studies in the section on overview of systematic reviews and meta-analysis. (10, 13, 39-42, 57, 73, 79). I also assessed the 29 case-control studies, (48, 51-60, 62, 66, 75-91) and 3 cohort studies (14, 17, 92-93). The list of excluded citations is shown. The difference in the citation count of included and excluded articles largely reflects excluded duplicate articles retrieved from the two databases. I also evaluated several studies (36, 37, 49, 64-68, 72, 94-109) which reported on the biological mechanisms that supported or refuted the causal association between talcum powder products and ovarian cancer.

IX.I. Overview of Systematic Reviews and Meta-analysis. Three meta-analysis were not preceded by a systematic search (57, 73, 79). There were 4 systematic reviews and meta-analysis which evaluated the link between perineal talc use and ovarian cancer (39-42) using summary data, while an individual participant data analyses pooled data from case-control studies in the Ovarian Cancer Consortium (10). Another systematic review and meta-analysis analysis conducted on behalf of the manufacturer only evaluated the use of cosmetic talc on

contraceptive diaphragms and ovarian cancer (13) and was not directly relevant to the causal question of genital talc use and the development of ovarian cancer, but was critically evaluated for strengths and weaknesses. The results of the methodologic assessment of each of these using the AMSTAR checklist is summarized in the Table 1. Two meta-analysis (13, 40) are of poor methodological quality. Regardless, the findings of older meta-analysis have been superseded given the publication of new meta-analysis. (41, 42).

1. In 1992, Harlow et al. combined crude odds ratios from their case-control study, discussed below with 5 pre-existing existing case-control studies (79) to evaluate the association between perineal talc exposure and ovarian cancer. The studies included 1106 cases and 1756 controls, with talc exposure reported among 50.7% of cases and 46.9% of controls. Using crude odds ratios from the individual studies, perineal exposure to talc was associated with a statistically significantly increased risk of ovarian cancer (OR 1.3, 95% CI: 1.1-1.6). Major limitations include the lack of a systematic search methodology.

2. A 1995, meta-analysis by Gross and Berg (39) was conducted on behalf of the manufacturer Johnson and Johnson. A search of PubMed issuing the terms “ovarian cancer” and “talc or cosmetic” identified 9 case-control studies and reported a statistically significant increased risk of ovarian cancer in both the crude odds ratio (1.27, 95% CI: 1.09-1.48) and adjusted odds ratio (1.31, 95% CI: 1.08-1.58). They also examined the odds ratio by tumor type and notes that all the analyses produced relative risks greater than 1 with confidence intervals that exceeded 1. Despite the statistically significantly increased risk seen in analyses, the authors concluded that the *“literature does not unequivocally support the hypothesis.... But [does] suggest the possibility of an increased risk of ovarian cancer due to perineal talc use.”* The description of study procedures was incomplete, and the search strategy was limited. The study was supported in part by the manufacturer.

3. Cramer et al. 1999 combined crude odds ratio data from their case-control study with pre-existing case-control studies in a meta-analysis of 14 total case-control studies, (57) and reported a statistically significant OR of 1.36 (95% CI: 1.24-1.49). The tests for statistical heterogeneity were not significant (p=0.085). Limitations include the lack of a systematic search.

4. Huncharek, for his 2003 publication, conducted a meta-analysis of 16 studies including 11,933 subjects. (40). They searched MEDLARS, Embase and Cancer Lit databases using search term “talc exp ovarian neoplasms.” They excluded studies on borderline tumors or those which did not report on types of perineal exposure (dusting vs sanitary napkins). The meta-analysis was conducted using adjusted measures of effect using the inverse variance method. It included 15 population-based and 1 hospital-based study and excluded the 1983 Hartge study. (76). The pooled analyses yielded a significantly increased risk of ovarian cancer (RR 1.33, 95% CI: 1.16-1.45) associated with the perineal use of talc without evidence of statistical heterogeneity. Seven studies reporting on the number of talc applications per month were evaluated where the highest risk category (RR 1.21, 95% CI: 1.00-1.45) and lowest risk category (RR 1.83, 95% CI: 1.55-2.15) reported an increased risk. In sensitivity analyses, hospital-based studies showed no statistically significant excess risk between talc use and ovarian cancer risk, i.e., RRs 1.19 (95% CI: 0.99-1.41) versus population-based studies which showed an increased risk (RR 1.38, 95% CI: 1.25-1.52), despite the proportion of controls using talc being similar across the two designs. The confidence intervals were overlapping suggesting that the findings were consistent. Recent updated meta-analysis discussed below report similar estimates from hospital and population based studies. (42). The RRs were relatively stable even after exclusion of the single cohort study or limiting the analysis to studies that controlled for body weight and BMI. The authors stated that the association between talc use and ovarian cancer could also be attributed to exposure misclassification among prevalent cases or side effects of treatment such as radiotherapy and chemotherapy which may predispose to talc use (“reverse causality”). Study limitations include the inability to conduct meaningful dose-response analysis because only nine of the 16 studies provided data on dose-response, with substantial differences in dose stratification levels among these studies.

5. Langseth reported on a meta-analysis of 20 case-control studies and one cohort study in 2008. The various case-control studies provided a significant excess risk (10 studies) and non-significant excess risk in 10 studies. (73). The prospective cohort study reported no association between cosmetic talc use and all types of ovarian cancer combined but showed evidence of an increase in serous tumors. The hospital-based case-control studies reported a pooled OR of 1.12 (95% CI: 0.92-1.36) and population-based case-controls studies reported a pooled OR of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using the fixed effects model was 1.35 (95% CI: 1.26-1.46).

6. Terry et al conducted an individual participant pooled analysis of eight case-control studies was conducted by the investigators for the Ovarian Cancer Consortium. (10). Genital powder use was defined as any powder use (talc, cornstarch, deodorizing) applied directly or indirectly (with sanitary pads, tampons or underwear) to genital, perineal or rectal area. Criteria for exposure varied from ever use to one year or longer. Women who reported both genital and non-genital powder use were considered genital users. Cumulative exposure was calculated by multiplying months of use by frequency of use. Never users and women who reported non-genital powder use were considered as the reference group. Analyses were adjusted for potential confounders such as age, duration of contraceptive use, parity, tubal ligation history, BMI and race/ethnicity. Family history of breast and ovarian cancer was not included in the final model. Genital powder use was reported in 25% of controls and 31% of cases. The rates of genital powder use varied widely between studies ranging from 15-45% in the control group. Ever regular uses of genital powder reported a statistically significantly increased risk of ovarian cancer (OR 1.24, 95% CI: 1.15–1.33) compared to non-users. There was no evidence of heterogeneity in the studies regardless of the reference group ($P_{\text{heterogeneity}}=0.61$). Results were similar when the reference group included those with genital powder use and never users. Risk was elevated for various histologic subtypes of ovarian cancer including invasive serous (OR 1.20, 95% CI: 1.09–1.32), endometrioid (OR 1.22, 95% CI: 1.04–1.43), and clear cell (OR 1.24, 95% CI: 1.01–1.52) tumors, and for borderline serous tumors (OR 1.46, 95% CI: 1.24–1.72). There was an increased risk of all nonmucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder use compared with nonuse: (OR_{Q1} 1.18, 95% CI: 1.02–1.36; OR_{Q2} 1.22, 95% CI: 1.06–1.41; OR_{Q3} 1.22, 95% CI: 1.06–1.40; OR_{Q4} 1.37, 95% CI: 1.19–1.58). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis ($P_{\text{trend}} < 0.0001$), no significant trend was seen when analyses were restricted to ever users ($P=0.17$). After excluding those with tubal ligation or hysterectomy, the results were similar. Restricting analysis to applications before tubal ligation made no substantive difference. There was an evidence of interaction by BMI, with the risk being higher for women with BMI $< 30 \text{ kg/m}^2$ (OR 1.28, 95% CI: 1.17-1.39) than women with BMI $\geq 30 \text{ kg/m}^2$ (OR 1.14, 95% CI: 0.98-1.32; $P_{\text{interaction}}=0.01$). There was no evidence of interaction by tubal ligation, parity, endometriosis or post-menopausal status. The association was similar for women who used powder during varying time periods (1952-1961; 1962-1972; and after 1972). The strengths of this meta-analysis include the use of individual participant data, which allowed them to conduct dose-response analysis and analysis by histologic subtype. The lack of statistically significant evidence on non-

mucinous cancer could be attributed to the low number of users, or talc may not be relevant to these tumor types which have different biological mechanisms. The limitations include the definition of exposure as genital powder user varied from ever user, ever regular user to powder use for at least 6 months or at least 1 year in the studies.

7. Berge et al. 2018, a meta-analysis of 27 studies (41) (24 case-control studies and 3 cohort studies) was conducted according to the Preferred Item for Reporting of Systematic Reviews and Meta-Analysis Guidelines. (110). The authors searched multiple databases including Pubmed, Embase and Scopus. They examined the citations independently and in duplicate. They rated the studies using the New Castle Ottawa scale for study quality. They conducted meta-regression for duration (RR for every 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency) for studies reporting at least three categories of duration or frequency after excluding the non-exposed category. Dose-response analysis was conducted using two methods. Study specific slopes were estimated from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model. The study specific estimates were pooled in a single meta-analysis in the second method. Six of the case-control studies were hospital-based and the remainder were population-based. Most of the studies were conducted in North America and Europe. They reported a statistically significant increase in risk of developing ovarian cancer with talc use (adjusted RR 1.22, 95% CI: 1.13-1.30). A statistically significant risk was seen in the case-control studies (RR 1.26, 95% CI: 1.17-1.35), whereas the excess risk in the cohort studies did not reach statistical significance (RR 1.02, 95% CI: 0.85-1.20; $P_{\text{heterogeneity}} = 0.007$). There was no difference between results for borderline (RR 1.27, 95% CI: 1.09–1.44) and invasive ovarian cancer (RR 1.20; 95% CI: 1.08–1.31). There was a trend in RR with duration and frequency of genital talc use and suggestion of dose-response. There was a statistically significant risk for only serous carcinoma (RR 1.24, 95% CI: 1.15–1.34) and no other histologic subtypes ($P_{\text{heterogeneity}}$ between histologic types was 0.04). Use of talcum powder in the “early” period showed increased risk of ovarian cancer (RR 1.18, 95% CI: 0.99–1.37). The use in the “late” period was higher (RR 1.31, 95% CI: 1.03–1.61; P-value for test for heterogeneity between the groups of studies was 0.37), arguing against the hypothesis that a higher risk would be seen only among those with earlier exposure during time-periods in which talcum powder was reported to contain asbestos. The cut-off points varied between studies was variable between 1970 and 1980. Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR 1.00; 95% CI: 0.84–1.16, and RR 0.75, 95% CI: 0.63–0.88, respectively).

Stratified analysis based on the adjustment for confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/ education, BMI) found no evidence of heterogeneity. Meta-regression using the two different approaches yielded similar results. Based on the two-step approach, a 10-year increase in genital talc use was associated with a RR of 0.97 (95% CI: 0.82–1.12; nine studies reporting on duration), whereas the RR for an increase of one application per week was 1.03 (95% CI: 0.82–1.25; five studies reporting on frequency). There was no evidence of publication bias on visual inspection of funnel plot and the Egger test ($P=0.7$), with the cumulative meta-analysis reporting stabilization RR of in the range of 1.20–1.25. Stratified analyses conducted did not suggest the possibility of residual confounding (i.e., higher adjusted estimates than unadjusted estimates).

There are some limitations to the analysis. While the role of selection and recall bias is a possibility, given higher estimates reported from recent studies, such biases should account for increase in recall for all histologic cancer subtypes and not just serous ovarian cancer. Importantly, the dose-response analyses analyzed duration and frequency separately and not the intensity of exposure (duration combined with frequency) or cumulative exposure to talc and the exclusion of the reference category from the dose-response curve diminished the power of the dose response analysis to detect any threshold effects.

8. Penninkilampi, et al. 2018 (42), the most recent and comprehensive meta-analysis which focused on studies with greater than 50 cases of ovarian cancer also reported on data from 26 case-control studies (13,421 cases and 19,314 controls) and 3 cohort studies (890 cases). The study was also conducted according to the PRISMA protocol and included a search of multiple databases (MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials) and LILACS. They also evaluated the quality of studies using the Newcastle Ottawa Scale. They also evaluated long term talc use in which OR were extracted for group with the longest duration of exposure compared to controls, if there was a minimum of 10 years of talc exposure. Lifetime applications within each study were divided into < 3600 lifetime applications (equivalent to less than 10 years) and >3600 applications or more than 10 years of exposure. The number of lifetime applications is a better marker of intensity of exposure compared to duration or frequency of exposure alone. They assessed publication bias using the failsafe method where the failsafe number is the number of studies missed to nullify the findings of meta-analysis.

This was a well-conducted analysis and some strengths and limitations are notable. They found all studies to be of reasonable quality and did not exclude studies based on study quality. None of the analyses in this review had statistically significant heterogeneity except for non-perineal application arguing for the consistency of estimates. Any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, 95 % CI: 1.24-1.39). Greater than 3600 lifetime applications were more associated with ovarian cancer than lifetime applications of less than 3600, although risks were significantly elevated in both groups. While the case-control studies reported a statistically significantly increased risk of ovarian cancer (OR 1.35, 95% CI: 1.27-1.43), the cohort studies reported an increased risk which was not statistically significant (OR 1.06, 95 % CI: 0.90-1.25).

9. Meta-analysis on Talc-Dusted Diaphragms and Ovarian Cancer. Another meta-analysis of 9 case-control studies by Huncharek et al. (13) reported on exposure to talc dusted diaphragms and ovarian cancer. On one hand, the authors dismissed the “talc hypothesis” for potential carcinogenicity, but then argued that talc dusted diaphragms was a more “intuitive model” for testing whether talc exposure increased the risk of ovarian cancer without any biological evidence (or references) to support this intuition. They searched MEDLARS, Cancer Lit and Current Contents. They included 9 studies and the pooled analyses yielded an excess risk of ovarian cancer which was not statistically significant (RR 1.03, 95% CI: 0.80-1.33). Exclusion of the study in which exposure to dusted diaphragms was assumed rather than measured further elevated the OR, which was not statistically significant (OR 1.12, 95% CI: 0.84–1.48) similar to a non-significant elevation in OR after the exclusion of the studies not published as full research articles.

This meta-analysis was flawed for several reasons. The most important limitation was its exclusive focus on talc powder dusted diaphragms as the route of exposure which could not inherently address the causal question of whether genital talcum powder dusting is associated with increased risk of ovarian cancer. As a result of this narrow hypothesis, they excluded several available studies that reported a statistically significant excess risk of ovarian cancer with perineal talc use. Several methodological flaws include the exclusion of the lowest category of exposure for some studies, (51) data extractions errors for others (56), and inclusion of ineligible studies that did not disaggregate data between talc and cornstarch users. (77) The study was by Johnson & Johnson and Luzenac America and was of poorer methodological quality than those conducted by their academic counterparts (43). As a result of these serious methodological

flaws, and the publication of several newer, higher quality meta-analysis with updated data, (10, 41, 42) the findings of this study have been superseded.

It is important to note here that while the AMSTAR checklist evaluates the methodologic quality of systematic reviews, several studies shown below were published prior to the publication of the AMSTAR checklist.

IX.II. Case-Control Summaries.

1. More than three decades ago Cramer et al. (75) evaluated 215 white women diagnosed with epithelial ovarian cancer identified through 12 hospitals in the greater Boston area. They were randomly matched by age, race and residence to 215 population-based controls. Surgical specimens were reviewed to confirm and classify tumors by histologic type. Talc exposure was determined through in person interviews. Multivariable logistic regression was used to estimate the Relative Risk. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls.

Adjusted for parity and menopausal status, this difference yielded a RR of 1.92 (95% CI: 1.27-2.89) for ovarian cancer associated with talc exposure. Women who had regularly engaged in both practices had an adjusted RR of 3.28 (95 % CI: 1.68-6.42; $P < 0.001$) compared to women with neither exposure. After adjusting for religion, marital status, educational levels, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use and smoking the RR was attenuated but remained statistically significant (RR 1.61, 95% CI: 1.04-2.49). The limitations of the study include the potential for selection bias in controls because of high rates of non-participation, although RR remained statistically significantly elevated even though the analysis was restricted to 121 cases matched with controls without a referral. Since approximately 50% of ovarian cancer cases in the Boston area was sampled, any potential for pervasive selection bias of cases was minimal. Other potential limitations include the adjustment for only a limited set of confounders such as parity and menopausal status.

2. Hartge et al. 1983 (76) conducted a hospital-based case-control study of women with pathologically confirmed primary epithelial ovarian cancers matched to equal number of women for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy in the same hospitals in Washington, DC. Controls were frequency matched for age, race and hospital. Exposure to talc was ascertained through questions about reproductive and sexual history, medical history, drug use, and other exposures. The questions for talc use were added after the study began yielding 135 cases and 171 controls.

Among the women users of talc in sanitary napkins, underwear, or the genital area there was an excess risk of ovarian cancer (unadjusted RR 2.5, 95 % CI: 0.7-10.0) which was not statistically significant due to small sample size (n= 7 cases and 3 controls). The limitations to the study include the limited number of cases and controls reporting genital use of talc (n=10) and publication as a letter to the editor which may or may not undergo peer review depending on editorial practices at the journal. They did not report adjusted results of ovarian cancer after perineal exposure to talc. Another limitation is the potential for recall bias; however, this was likely minimal given similar reporting of douching practices in cases and controls.

3. In 1988, Whittemore et al. (58) evaluated 188 pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center. The diagnoses were subsequently histologically verified. One group of controls was selected from the hospital (n=280); and a second group was selected from the population using random digit dialing (n=259). Exposure to talcum powder products was determined through a structured in-person interview at home where subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Data was recorded by type (perineum, sanitary pads, diaphragm or some combination thereof), and duration of use.

Population cases were more likely to be younger and more likely to be premenopausal than cases and hospital-based controls. Approximately 52% of cases reported talc use compared to 46% controls (RR 1.40, p=0.6). After adjusting for parity and oral contraceptive use, perineal use of talc was associated with an excess risk of ovarian cancer that was not statistically significant (RR 1.45, 95% CI: 0.812.60). Women who used talc an average of 1-20 times per month reported an excess risk in comparison to those who used it less frequently which was not statistically significant (RR 1.27, p=0.29). The risk among users of more than 20 times per month was 1.45 times greater than non-users, but the findings were not statistically significant (p=0.09). The overall increased risk in overall applications per month was 1.30 (p=0.19).

Although the data showed a *trend* of increasing risk with increasing frequency of perineal exposure, the trends were not statistically significant and there was no trend with increasing duration of exposure. The risk of ovarian cancer with talc use between one and nine years was 1.6 times the risk of those with a shorter duration (95% CI: 1.00-2.57; p=0.05), and the risk among those with more than 10 years of exposure was 1.11 higher than that of non-users (95% CI: 0.74-1.65; p=0.61).

The limitations of the study are the inability to interview cases and the choice of two controls. Some amount of non-differential misclassification of exposure may bias findings towards null. The dose-response analysis was limited by the inability to determine the combined effect of frequency and duration of exposure. The study reported a statistically increased risk of ovarian cancer with coffee consumption and a non-significant reduction in risk with smoking. Subsequent meta-analysis (111) or Mendelian randomization (112) studies have confirmed that there is no association between coffee consumption and ovarian cancer, whereas smoking has a heterogeneous relationship to ovarian cancer which varies by histologic subtypes. (112) The reports of such additional spurious associations suggest an element of measurement error in their database.

4. Harlow et al. 1989 (77) conducted a population-based case-control study which included 116 females 20-79 years old with *serous and mucinous borderline ovarian tumors* identified using International Classification of Disease (ICD)-9 codes from the cancer registries of three western urban counties in Washington State. An independent pathology review confirmed diagnosis for 73% of tumors with 94% agreement, so the additional 33 cases were included. A sample of 158 controls of white women was identified through random digit dialing. Women with bilateral oophorectomy were excluded from the analysis. Any exposure to talc including any perineal exposure to powder, method of use, type of powder use (cornstarch, baby powder, talc, deodorizing powder), and combinations of method and type was ascertained through in-person interviews.

The study reported no statistically significant increased risk of ovarian cancer with perineal use of dusting powders (RR 1.1, 95% CI: 0.7-2.1). When looking at unspecified talc adjusted for the same factors, the RR was 1.0 (95% CI: 0.4-2.4). However, women who reported any use of talc containing powder on sanitary napkins showed an excess risk which was not statistically significant due to limited statistical power (RR 2.2, 95% CI: 0.8-19.8). However, among the sample of women who used deodorizing powders alone or in combination with talc, the risk of ovarian cancer was RR 2.8 (95% CI: 1.1-11.7) attributed to the potential exposure to asbestos. The limitations to the study include the potential for selection bias since 30% of cases and controls did not participate, although their characteristics were like the included participants which may have limited any impact. It is also possible that these findings are limited to borderline rather than malignant ovarian cancers.

5. In 1989, Booth et al. (51) conducted a population-based case-control study of 280 cases of ovarian cancer in women under 65 years of age from 13 hospitals in London and two in

Oxford. 451 controls were selected from other hospitals as enough age-matched controls were unavailable. The study included both pre- and post-menopausal women. Ovarian cancer was determined through hospital diagnoses with pathological specimens being histologically classified. Serous tumors were most prevalent, though mucinous, endometrioid and clear cell carcinoma was included. Information regarding talc exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly, or daily talc use.

After adjusting for age and social class (based on occupation of the husband for married women, and their own occupation for women who were not married) talc users reporting use more than once a week had a higher risk compared to never users. (RR 2.0, 95 % CI: 1.3-3.4). Those who reported daily use also had a non-significantly higher risk (RR 1.3, 95% CI: 0.8-1.9). There was some amount of missing data (8% of cases and 4% of controls), and no consistent trend of increasing risk with increasing frequency of use. However, data was not available on the duration of talc exposure to conduct meaningful dose-response analysis.

6. In 1992, Harlow et al. (79) included 235 cases of white women between the ages of 18 and 76 who had been diagnosed with ovarian cancer at one of 10 hospitals in the Boston metropolitan area. Controls were randomly selected from the town books; annual publication lists and address lists within 2 years of the age of case as potential controls. Cancer was confirmed through an independent pathology review. Talc exposure was determined through in-person interviews. Talc exposure from infancy with diapering, or use on other parts of the body, was not included. Talc use in other parts of body was considered unexposed. Talc use was reported as any genital application, type of application (sanitary napkin/underwear, via partner or application to diaphragm, via dusting to perineum), number of applications per month, years of use, age at first use, years since last use, whether use was before or after 1960, brand of application, estimated total lifetime applications, estimated applications excluding use after hysterectomy or tubal ligation, and estimated applications excluding use after hysterectomy or tubal ligation and use during nonovulatory months. The Chi square test for change in linear trend based on change in deviance in models.

Most participants reported use of baby powder. Perineal talc use was associated with an increased risk for ovarian cancer (OR 1.5, 95% CI: 1.0-2.1) when adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight. Perineal use of talc via dusting powder to perineum was associated with a significantly increased risk of ovarian cancer OR 1.7 (95% CI: 1.1-2.7), whereas use by sanitary napkins, underwear, use via

diaphragms was not associated with a significantly increased risk. Adjusted risk was highest for endometrioid tumors (OR 2.8, 95% CI: 1.2-6.4) and borderline tumors. A greater proportion of women with endometrioid tumors reported more than 10,000 lifetime applications of talc during ovulatory cycles while having an intact genital tract compared to other histologic types (34 % vs 16%, respectively). The risk of cancer increased significantly with increased frequency of applications per month using a linear test trend as a continuous variable. The risk was highest among the women who applied talc once daily relative to non-users. Women who applied talc for more than 10 years were at 60% greater risk for ovarian cancer relative to non-users. An 80% excess risk was associated with an estimated exposure of more than 10,000 applications. The association between talc and ovarian cancer was greater than in talc products before 1960. Restricting the analysis to exposure during ovulatory months, women with intact genital tract and more than 10,000 applications during ovulatory cycles had a threefold increase in risk of ovarian cancer. Limitations included the high rates of non-response (n=31% cases and 19% of controls) and failure to adjust for family history of ovarian cancer and oral contraceptive use.

7. Chen et al. 1992 (78) evaluated 112 cases of ovarian cancer in Beijing China. The diagnosis was confirmed by laparotomy and pathological examination. Serous cancer accounted for 51% of cases, mucinous for 19%, and miscellaneous epithelial for 30% of cases. Two controls were matched for each case using random selection from the same street, office, or township. A comprehensive questionnaire was administered through face-to-face interviews and collected information about menstrual, obstetric, marital, medical, familial, and dietary histories with reference to events 3 years or more prior to diagnosis. A total of 224 controls were selected. Talc exposure was measured through a yes or no metric, for exposure occurring 3 or years prior to date of diagnosis or equivalent date in controls. Logistic regression was conducted to estimate relative risk.

The mean age of participants was 48.5 and 49 years among cases and controls respectively. After adjusting for education and parity, there was an excess risk of ovarian cancer associated with a history of long-term (>3 months) application of dusting powder to the lower abdomen and perineum (RR 3.9, 95% CI: 0.9-10.6) which was not statistically significant due to limited statistical power (n=7 cases and 5 controls reporting powder use). The limitations of the study include the small sample size, loss to follow up and death, the inability to fully ascertain all cases of ovarian cancer and the exclusion of controls with other health problems. Although the applicability of these findings from a Chinese population to a US population is limited, the

findings of an increased risk in different parts of the world provide evidence in support of an increased risk of ovarian cancer with dusting powder use.

8. In 1992 Rosenblatt et al. (80) conducted a hospital-based case-control study of the association between genital and respiratory talc exposure and the development of epithelial ovarian cancer at the Johns Hopkins Hospital. Among 140 diagnosed cases of epithelial ovarian cancer, approximately 108 were successfully interviewed. Seventy-seven pathologically-confirmed incident cases diagnosed within 6 months of admission were matched to age-race matched controls (n=46). Exposure was ascertained using a structured questionnaire administered at home and in the hospital. Conditional logistic regression was used to obtain strength of the association.

Although genital powder use was not associated with an increased risk of ovarian cancer, statistically significant increased risk was observed for exposure to talc on sanitary napkins (OR 4.79, 95% CI: 1.29-17.79) after adjusting for confounders such as obesity, socioeconomic status, religion, reproductive status and oral contraceptive use, with a smaller risk after genital bath exposure (RR 1.7, 95% CI: 0.7-3.9). An excess risk of borderline significance was seen for exposure of ≥ 37.4 years (RR 2.4, 95% CI: 1.0-5.8). The limitations include the small sample size, lack of data on frequency of talc use, and the limited generalizability of the findings from one hospital. The control group also reported a very high rate of talc use (90%) which may have limited the ability to detect any differences.

9. In 1993, Tzonou et al. (81) reported on a hospital-based study of 189 women under 75 years of age with histopathologically confirmed ovarian cancer in Athens, Greece compared with 200 hospital visitor controls in two hospitals. Control patients were those hospitalized in the same ward as cancer cases. Talc exposure was determined by asking participants to report talc use (over an extended period before the onset of illness for cases and for a comparable period among controls) among other characteristics, through interviews in the hospital. Talc use was reported as a yes/no metric. Estimates were adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status and age at menopause, parity and age at first birth, tobacco smoking, coffee drinking, consumption of alcoholic beverages, hair dyeing and mutual (analgesics-tranquilizers/hypnotics) tranquilizers.

An exceedingly small number of cases (n=6) and controls (n=7) reported perineal use of a talc. There was no statistically significant increased risk of ovarian cancer associated with perineal application of talc (RR 1.05; 95% CI: 0.28 to 3.98). The limitations of the study include the low

proportion of talc exposure, which was ascertained in only approximately 3% of cases and controls.

10. In 1995, Purdie et al. (82) evaluated 824 histologically confirmed cases of epithelial ovarian cancer and 860 controls from gynecological oncology treatment centers in the three most populous Australian states. Controls were selected from electoral rolls in Australia where electoral participation is mandatory using a random procedure to match the age distribution of cases. Talc exposure was determined through face-to-face interviews conducted by trained interviewers using a standard questionnaire.

After adjusting for parity, there was a statistically significant increase risk of ovarian cancer reported with talc use on the abdomen or perineum (OR 1.27, 95% CI: 1.04-1.54). The limitations include high non-response rates in controls which may differ from the source population, but the age distribution of controls was like non-responders suggesting minimal response bias by age. There is also the possibility of bias in the selection of cases. They only adjusted for a limited set of confounders. Some misclassification of outcome is also possible given borderline and malignant cases were lumped together, although no differences were found when results were analyzed separately. Recall and interviewer bias was minimized by trained interviewers who administered standardized questionnaires.

11. In 1996 Shushan et al. (83) reported on findings from a study of two hundred living cases aged 36-64 years with history confirmed diagnosis of primary invasive or borderline invasive ovarian cancer in the Israel Cancer registry. There were 408 women from the same area selected by random digit dialing. Both were interviewed using standardized questionnaires.

A larger proportion of cases than controls reported using moderate to a large amount of talc (10.5% vs 5.6%; $P=0.04$) compared to never users or seldom users, a difference which was statistically significant. Limitations include high refusal rate for cases (30%), the low rates of talc exposure among controls and limited adjustment for confounders. (14)

12. In 1997, Cook et al. (84) reported on 329 white women between the ages of 20-79 diagnosed with epithelial and borderline ovarian cancer identified through the Cancer Surveillance System of Western Washington. Women were randomly selected as controls using random digit dialing from a larger pool of women for cancer studies. Genital powder exposure was collected through structured in person interviews and reported as any lifetime powder application, method of use (perineal dusting only, diaphragm only, sanitary napkin only, or genital deodorant spray only). Additional exposure information included cumulative

lifetime days of use for dusting and similar metrics for other methods of use. Genital powder use was also separated into use of talcum powder, baby powder, cornstarch, deodorizing powder, bath/body powder, or unspecified powder. Analysis was presented by age because adjustment for other confounders such as income, marital status, body mass index, oral contraceptive or parity did not change results.

Genital powder exposure was more common among cases (50.8%) than controls (39.3%). After adjusting for age, any use of genital powder was associated with a statistically significant increased risk of ovarian cancer (RR 1.5, 95% CI: 1.1-2.0) compared to non-use, although there was no clear pattern of increasing risk after increasing duration of use. After adjusting for age, exclusive use of perineal dusting was also associated with a statistically significant increased risk of ovarian cancer (RR 1.8, 95% CI: 1.2-2.9), whereas the risks for use via other routes of exposure (e.g. diaphragms, powder) were not significant. There was a statistically significant increased risk of serous tumors associated with any genital powder application (RR 1.7, 95% CI: 1.1-2.5), but not for the smaller number of mucinous or endometrioid tumors. Limitations include low participation rates (64.3% for cases, 68% for controls), the potential for recall bias, and confounding by family history of ovarian cancer in a study where more than 50% of controls were less than 45 years of age.

13. In 1997, Chang et al. (56) conducted a population-based case study of cases of borderline and invasive histologically confirmed ovarian cancer among participants aged 35 to 79 years from Canada. Talc exposure was determined through a questionnaire conducted during an in-home in person interview to detail medical and reproductive histories. Powder use was reported as talc, cornstarch, or a mixture. Information was provided for type of exposure, number of uses per month, years of use, years of use pre- and post-1970, and well as years of use before and after a tubal ligation or hysterectomy. They adjusted for age, years of oral contraceptive use, number of full-term pregnancies, duration of breastfeeding per pregnancy, tubal ligation, hysterectomy, and having a mother or sister with breast or ovarian cancer.

Talc exposure was reported in 44% of cases and 35.6% of controls. After adjusting for confounders there was a statistically significantly increased risk of ovarian cancer associated with any talc exposure via sanitary napkins, direct application to the perineum or both (OR 1.42, 95% CI: 1.08-1.86). The dose-response analysis showed a borderline-significant association was detected between duration of after-bath talc exposure and risk (OR 1.09, 95% CI: 0.98-1.21, per 10 years of exposure), without any significant association between frequency of exposure and

risk. Although risk was elevated for both invasive and borderline carcinomas, it was statistically significant only for invasive carcinoma. The limitations of the study include the potential for recall bias and the high rates of non-response (28.7% for cases and 35.5% for controls)

14. Green et al. 1997 (62) conducted a population based case-control study of 824 women aged 18-79 with histologically confirmed ovarian cancer compared to 824 controls. The methods and limitations were similar to the study by Purdie et al. (82). The prevalence of talc use was approximately 40% in the control use. Perineal talc was significantly associated with ovarian cancer (RR 1.3, 95% CI: 1.1-1.6), without any effect of longer duration of talc use. Compared to women who had neither used talc nor had sterilization, the risk was highest among talc users without surgery like the findings by Whittemore et al. (58). There is the potential for recall bias, and the quantity of talc use was unknown.

15. In 1998, Godard et al. (85) examined 170 French-Canadian women with a histologic diagnosis of ovarian cancer from 2 large Montreal teaching hospitals. Cancer diagnoses were histologically confirmed, and pathology reports were reviewed for tumor classification. 170 population-based controls were identified using modified random digit dialing to match the age distribution of cases. Talc exposure was obtained through a 57-item questionnaire. 70% of interviews were conducted in person in clinics and 30% were conducted via phone. Talc use was reported through an ever/never metric for perineal use.

Only 10.6% of cases and 4.7% of controls reported talc use. As a result, perineal talc use was associated with an increased risk for ovarian cancer which was not statistically significant (RR 2.49, 95% CI: 0.94-6.58; $P = .066$) because of limited statistical power. Similar patterns of excess risk which did not reach statistical significance were seen in both the comparisons for sporadic and familial cases and controls. The limitations of the study include a modest non-response rates among cases (13%) and controls (10.7%).

16. In 1999, Cramer et al. (57) evaluated 563 ovarian cases identified through tumor boards and statewide cancer registries in Massachusetts or New Hampshire in a population-based control study. Pathology reports were reviewed, and slides were sought in any case where there was a discrepancy between histologic description and final diagnosis. Controls were selected from the population using random digit dialing with a response rate of 72% among eligible controls. Talc exposure was obtained through questionnaires in which potential controls and cases were blinded. Specific hypothesis regarding talc use were not discussed. Exposure was assessed prior to 1 year before date of diagnosis or date of interview for

controls. Talc use in the genital or rectal area, on sanitary napkins and on underwear was considered as exposure whereas non-use and non-genital use was considered as unexposed. Exposure from condoms and diaphragms was not assessed.

Genital talc exposure was reported in 27% of cases and 18.2% of controls and the average duration of talc use exceeded more than 20 years in cases and controls. There was a statistically significantly increased relative risk of ovarian cancer with genital talc exposure 1.60 (95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, or primary relative with breast or ovarian cancer. The highest risk was seen among women whose age at first use was between 20 and 25 (RR 1.87, 95% CI: 1.03-3.39) those who have used talc for less than 20 years (RR 1.86, 95% CI: 1.16-3.00), those whose total applications is less than 3000 (1.84, 95% CI: 1.12-3.03), women who used talc when nulliparous (RR 2.80, 95% CI: 0.64-12.20), and those with serous invasive tumors (RR 1.70, 95% CI: 1.22-2.39). Only one case and 3 controls reported primarily using cornstarch, these numbers are likely accurate for talc use, despite the potential for including other kinds of powders. There was little evidence of effect by confounders such as age, oral contraceptive use and parity. Linear trends were significant in models that included women who were not exposed without any clear trend in duration or intensity of exposure in models that excluded women who were not exposed. Analysis of dose-response censured after closure of female tract or non-ovulatory cycles, and models showed a trend this was statistically significant only after inclusion of non-genitally exposed categories ($P_{\text{trend}}=0.022$).

Potential limitations include the potential for recall bias, although this is likely to be minimal and more likely to occur for short term exposures rather than long term exposures. The evidence for substantial degree of recall bias is refuted by the findings that there is no evidence of higher proportion of perineal talc exposure reported among cases in more recent compared to older studies to suggest stimulated reporting, no evidence of significant excess of non-genital talc exposure among cases, and the excess is limited to invasive serous carcinoma,(84) rather than all types of ovarian cancer or endometrial carcinoma.

17. In 1999, Wong et al. (86) reported-on a hospital-based study of 499 patients with epithelial ovarian cancer and 775 age-matched controls with non-gynecologic cancer diagnoses. Cancer diagnoses were confirmed in the cancer registry. Exposure was ascertained through self-administered questionnaire in which approximately 15% of participants did not respond to questions about talc use or its frequency.

Talc use was reported by 47.8% of cases and 44.9% of controls. Genital talc use was reported by 34% of cases and 32.2% of cases. The mean duration of talc use was 22 years in controls and 21 years in the study population. After adjusting for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy there was no statistically significant increased risk of ovarian cancer among ever users of talc (OR 0.92, 95% CI: 0.24-3.62). There was no significant association between duration of use and development of ovarian cancer even after prolonged exposure of more than 20 years. However, when evaluating genital talc use via histologic subtypes of cancer, all ORs were above 1 (except for undifferentiated carcinoma) but were not statistically significant. Similarly, those who had no history of genital tract interruption the ORs were elevated but not statistically significant. However, the study was limited by the non-response rate and the choice of a controls with malignancies. (113). Additionally, data on exposure were reported on a self-administered questionnaire rather than administered by interviewers. The results could not rule out the effect of talc exposure via condom use and data was not available on the frequency of talc use.

18. Ness et al. (87) conducted a population-based control study. Cases (20-69) years of age with recent diagnosis of ovarian cancer (n=) were compared with community-based controls 65 years or younger through random digit dialing. Controls were age-matched as well as matched by last 3 digits of the phone number. Approximately 72% of controls were selected. As a part of detailed interviews with calendars women were asked about their reproductive history including talc use. The question was, "As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least once per month for 6 or more months on your: 1) feet, arms, or breasts, but not the genital or rectal areas? 2) genital or rectal area? 3) on your sanitary napkins? 4) on your underwear? 5) on your diaphragm or cervical cap?" They were then asked whether they had a male sexual partner(s) for more than a year who regularly used such products on his genital area or underwear. The duration of use of talc for each of these modes of use was also queried. The estimates were analyzed using conditional logistic regression after adjusting for age and gravidity (each as continuous variables), race (white/black/other), history of ovarian cancer in any first degree relative (yes/no), oral contraceptive use (yes/no), tubal ligation (yes/no), hysterectomy (yes/no), and breast-feeding (yes/no).

Talc use was reported in 53.2 % of controls. Compared to never talc use, talc use on all parts of the body (OR 1.4, 95% CI 1.1-1.6), genital/rectal (OR 1.5, 95% CI 1.1-2.0) on sanitary napkins

OR 1.6, 95% CI 0 1.1- 2.3) and underwear OR 1.7, 95% CI. 1.2-2.4) was associated with a statistically significantly increased risk of ovarian cancer after adjusting for confounders. However, talc use on diaphragms (OR 0.6, 95% CI 0.3-1.2) or by male partner (OR 1.0, 95% CI 0.7 to 1.4) was associated with an increased risk which was not statistically significant. Although duration of talc use did not show a pattern of increased risk with increased risk with duration of exposure, the OR for each categories (> 1 year, 1-4 years, 5- 9 years and > 10 years) were elevated and were statistically significant for 1-4 years. Tubal ligation and hysterectomy decreased ovarian cancer risk. Limitations to the study include the low response rates among cases and controls due to exclusion of prevalent ovarian cancer. Recall bias while always a concern was less likely to be a concern given that risk factors overall did not increase risk but were limited to those linked to inflammation.

19. In 2004, Mills et al. (59) conducted a population-based case-control study of 256 women with histologically confirmed incident epithelial ovarian cancer from 22 counties in Central California. They also selected 1122 controls who were residents of that area who had one intact ovary and no history of ovarian cancer. Talc exposure was determined through phone interviews conducted by trained interviewers. Talcum powder use in the genital area was reported as an ever/never metric, as well as by frequency, duration, and cumulative use. The final parsimonious model adjusted for age, race, duration of oral contraceptive use and breast feeding.

The rates of talc use in controls was 37.1 % and higher among white non-Hispanics. Controls were more likely to have been outside the US. Most of talc exposed cases and controls were non-white. There was a statistically significant risk of ovarian cancer associated with genital talcum powder use (OR 1.37, 95% CI: 1.02-1.85) after adjusting or age, race, duration of oral contraceptive use, and breast feeding. Although increasing frequency of use showed a 74% increased risk among women who used talcum powder more than 4-7 times per week ($P_{\text{trend}}=0.015$), this risk was not monotonic because risk the decreased between second (rarely to several times per month) and third categories (1 to 3 times per week). Duration of use also showed increasing risk and peaking between 4-12 years of use and declining thereafter ($P_{\text{trend}}=0.045$). Cumulative exposure increased in the second and third quartiles of exposure but declined among the highest quartile of users ($P_{\text{trend}}=0.051$). The risk was highest among those who had stopped using talcum powder in the last 1-2 years compared to those in the more distant past. The risks were primarily elevated for serous and mucinous tumors. Risk was higher among those reporting use after 1975 which may be related to the recency of use, and those after age 20. Limitations of the study include a low response fraction which was only

40% for eligible cases and 57% for eligible cases, and high rates of non-participation- 34.2% among cases and 29.3% among controls. The dose-response analysis did not exclude exposure during non-ovulatory periods or after gynecologic surgery which may have diluted the relative risk estimates. However, strengths include the ability to rule out prevalent cases by examining incident cases alone.

20. In 2004, Langseth et al. (88) conducted a case-control study of pulp and paper workers from different mills in Norway. Only one of these mills reported use of fibrous talc. They included 46 cases and reviewed histological records for each case. Most of the cases were invasive tumors. Four controls free of ovarian cancer and having intact ovaries were matched by birth year +/- 2 years and were drawn by incidence density sampling. A total 179 controls were available for analysis. Talc exposure was determined through personal interviews which took place in mill offices, at home, at a medical institution, or by phone. Talc exposure was reported environmentally and as use by personal hygiene (diapers, sanitary napkins, non-genital area or husbands use in genital area)

Talc exposure was reported among 50% of cases and 48% of controls. After adjusting for number of children, breastfeeding, age at birth of first and last child, age at menarche, age at menopause, smoking, and family history the use of talc use by personal hygiene was associated with an excess risk of ovarian cancer OR 1.15 (95% CI: 0.41-3.21), which was not statistically significant. The study has significant limitations. The sample size of the study was low with limited statistical power to detect a two-fold increased risk with a probability of only 53 % and response rate for interviews were low -76.1% for cases and 65.7% for controls. The inclusions of non-genital or husband's use in genital area among the exposed category diluted the estimates of relative risk for ovarian cancer associated with talc exposure. More information on cases was collected from relatives than controls because 71.5 of cases were deceased compared to only 28.6% of controls. The rates of missing data on talc use was high, because it was obtained from proxy respondents introducing an element of uncertainty in the estimates for relative risk of ovarian cancer associated with talc use.

21. In 2008, Merritt et al. (89) reported on a population-based study of 1,576 women with epithelial ovarian cancer as part of the Australian Ovarian Cancer Study. Pathology reports and diagnostic slides were reviewed for a sample of 87 women with 97% agreement with original abstracted data. Cases were confirmed by histopathology. 1509 controls were selected from the electoral rolls and were matched by age and residence. Talc exposure was identified through a comprehensive health and lifestyle questionnaire. Talc use was reported as

ever/never for perineal use (powder or talc in the genital area or on underwear or on sanitary napkins), years of use prior to surgery, use post-surgery, and use stratified by age at diagnosis. All analyses were conducted for talc use while the reproductive tract was patent and exposure occurring 12 months prior to the diagnosis of cases and similar period in controls was excluded.

The rate of talc use was 43% among controls and 46% among cases. When adjusted for age, education, parity, and oral contraceptive use of talc in the perineal region among women with patent tubes there was a statistically increased risk of ovarian cancer (OR 1.17, 95% CI: 1.01-1.36) with the highest risk reported for serous tumors (OR 1.21, 95% CI: 1.03-1.44). The tests for trends for duration of use were of borderline statistical significance for all cancers and serous subgroup ($P_{\text{trend}} = 0.02$ for both). No significant associations between number of years used pre- or post-surgery and significantly elevated risks for overall cancer and serous ovarian cancer were seen in women both above 70 years of age, and below 50 years of age suggesting that timing of talc exposure (before or after 1976) did not affect results. There was no association between PID and the risk of ovarian cancer or the protective effect of NSAIDs. Limitations include low response rates and the lack of data on the frequency of exposure.

22. In 2008 Gates et al. (55) conducted a nested case-control study as part of the New England Case-Control study and the Nurses' Health Study (NHS). Further cohort analysis from the NHS are presented in the section on cohort studies below. **Section IX.III.I** Ovarian cancer diagnoses were confirmed by the researchers. They included 1385 cases and 1802 controls. 76.7 % of cases were incident with respect to the timing of DNA collection in the NHS. Exposure was assessed through a questionnaire that asked questions related to use of talcum powder. The NECC questionnaires included questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or non-genital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week, or daily) or to sanitary napkins (yes/no). The study defined regular genital talc use as application of powder to the genital/perineal region at least once per week. We also created a categorical variable for frequency of talc use, using the categories from the NHS questionnaire.

Most of the participants were white. Regular genital talc was reported among 56 cases and 44 controls, and daily genital talc use reported among 35 cases and 25 controls, respectively. There was a statistically significant increased risk of total epithelial ovarian cancer (RR 1.36, 95% CI: 1.14-1.63; $P < 0.001$) and of serous invasive subtype (RR 1.60, 95% CI: 1.26-2.02) associated with regular use of talc when adjusted for age, study center, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of hormone use. The New England Case-control study had a higher RR associated with genital talc use than the Nurses' Health which had a smaller sample size. There was a statistically significant trend between increasing frequency of talc use and risk of both total and serous invasive ovarian cancer in the pooled analyses ($P_{trend} < 0.001$ for both total and serous invasive ovarian cancer). The association between talc and ovarian cancer was stronger among women with the glutathione S-transferase M1 (GSTM1) null genotype ($P_{interaction} = 0.03$), particularly in combination with the GSTM1 present genotype alone ($P_{interaction} = 0.03$) in two independent study populations. The strengths of the study include robust findings from two independent study populations. Although talc exposure was only measured in the 1982 NHS questionnaire when participants were between 36 to 61 years of age, the number of users who began talc use after this is likely small as shown by the fact that more than 95% of controls with regular talc in the NECC reported talc use before age 35. The consistent findings from the prospective NHS study and the NECC may have minimized any potential biases due to the case-control design. Since talc exposure was defined as at least once per week, such habitual exposure is less susceptible to recall bias than sporadic exposure.

23. In 2009, Wu et al. (48) conducted a population-based study of 609 cases of women and 688 controls between the ages of 18 and 74 residing in Los Angeles with histologically confirmed incident invasive or borderline ovarian cancers. Cases were identified through the Surveillance, Epidemiology and End Results (SEER) Program. Cases were matched to neighborhood controls on age and race/ethnicity. Controls were women with one intact ovary with no history of cancer except non-melanomatous skin cancer matched on age and race/ethnicity. Talc exposure was determined through a detailed interview by the same person which included a comprehensive questionnaire that used a reference date of 2 years before the date of diagnosis (or date of interview for controls). Talc use was reported as a yes or no metric (including yes or no for perineal area use), frequency and duration, total times of use, and total times of use before and after 1975. Few users of talc (24) had tubal ligation or hysterectomy prior to talc use and were considered as non-users.

The cases were primarily white woman but also included 41 African American women, 136 Hispanic women, and 51 Asian women. After adjusting for race, age, education, tubal ligation, family history, menopausal status, use of oral contraceptives, and parity perineal use of talc was associated with a statistically significantly increased risk of ovarian cancer (RR 1.53, 95% CI: 1.13-2.09). Elevated risks were also noted among those who used it on sanitary napkins, underwear and on diaphragms but not significant due to limited statistical power. There was a clear trend of increasing risk with increasing frequency of use among users who had used it for more than 20 years. The risk of ovarian cancer increased significantly with increasing frequency and duration of talc use; compared to never users, risk was highest among long duration (20 years), frequent (at least daily) talc users (RR 2.08, 95% CI: 1.34-3.23). The risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975 ($P_{\text{trend}} < 0.001$). The association between talc use and ovarian cancer was strongest for serous ovarian cancer. Risk of ovarian cancer increased with the diagnosis of endometriosis. Limitations include the rates of non-response among cases and controls, and classification of talc use among a small number of users with prior hysterectomy as being non-exposed. However, the effect of this misclassification is likely to be minimal.

24. In 2009, Moorman et al. (90) reported on a study involving 1,114 cases with histopathologically confirmed tumors as part of the North Carolina Ovarian Cancer Study. newly diagnosed cases were identified through the North Carolina Central Cancer Registry. All cases were confirmed by histopathologic review. Controls were frequency matched to cases and recruited from the same geographic region using random digit dialing. The controls could not have had a bilateral oophorectomy. Talc exposure was reported through in-person interviews conducted by nurses with life calendar and pictures of contraceptives, menopausal hormones, and other medications were used to help aid recall. Talc use was reported as a yes/no metric.

The analysis focused on invasive ovarian cancer which comprised of 78% of cancers for African-Americans and 79% for whites. Among controls, talc use was reported by 23.9% among whites and 31.2% of African-Americans. After adjusting for age there was an excess risk reported for both whites (OR 1.04, 95% CI: 0.82-1.33) and African Americans (RR 1.19, 95 % CI: 0.68-2.09) which were not statistically significant. Limitations include the high rates of non-response (33.5% among cases, 39.1% among controls), with higher non-response rates among African-Americans. There was a large proportion of missing data on talc use for cases and controls; 23.6% and 38.5% among whites, respectively, and 25.2% and 29.1% among African Americans, respectively, resulting in misclassification of exposure. The authors did not

clarify the route of talc exposure and may have classified non-genital talc exposure to the talc exposed group which may have diluted the RR. Additionally, the study did not adjust for confounders to address the timing, frequency and duration of talc exposure, or whether talc exposure occurred before or after tubal ligation or hysterectomy.

25. In 2011, Rosenblatt et al. (60) reported on a study of women between the ages of 35 and 74 from 13 counties in Washington state. Cases of borderline or invasive epithelial ovarian cancer were identified through the Cancer Surveillance System. Controls were selected from the population using digit dialing. Talc exposure was determined through in person interviews which included a reference period of unstated length before diagnosis or interview. For powder use on sanitary napkins and deodorant spray, the total number of months of use was recorded. For powder use on perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Talc use was reported as genital powder exposure by type of use, duration of use, lifetime applications, age at first use, age at last use, calendar year of first use, time since first use, and time since last use.

Perineal use of powder after bathing was reported in 12% of controls. Reporting of cornstarch was uncommon in the study. After adjusting for age, calendar year of diagnosis, county of residence, number of full term live births, and duration of hormonal contraception the perineal use of powder after bathing was associated with an increased ovarian cancer risk (OR 1.27, 95% CI: 0.97-1.66) which was not statistically significant, but a statistically significant increased risk was seen among women with borderline tumors (OR 1.55, 95% CI: 1.02-2.37), similar to that reported by Harlow et al. (79) There were no differences in risk among various types of powder use, as the risk among those who reported use of talcum powder was RR 1.38 (95% CI: 0.77-2.47). There was no difference in exposure outcome relationship between talc use before and after 1980. There was no pattern of risk associated with perineal dusting powder and the increasing extent of use as defined by years in which it was used or number of lifetime applications. The participation rate of cases and controls was modest at 76.8% and 69%. Some misclassification of exposure is possible as participants may be unable to provide accurate information on whether the specific powder contained talc. However, the presence of talc, rather than a specific dose, is the primary determinant of exposure in which case genital powder use is a reasonable proxy for talc exposure.

26. Kurta et al. 2012 (91) reported on a case-control study from the Hormones and Ovarian Cancer Project using 902 ovarian cancer cases and 1802 controls. Participants were diagnosed with histologically confirmed ovarian, fallopian tube or peritoneal cancers. They were at least

9 years old and within 9 months of diagnosis. Controls were frequency matched by age and area code to cases at 2:1 ratio. Trained interviewers collected data via questionnaires. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins or underwear or on diaphragms or cervical caps.

Perineal talc use was reported among 20.9% of controls and 27.6% of cases. After adjusting for age, race, education perineal talc was associated with a statistically significantly increased risk of ovarian cancer OR 1.40 (95% CI: 1.16-1.69). Limitations include the population which was women seeking treatment for infertility which may limit generalizability.

27. In 2015, Wu et al. (53) evaluated 1,701 newly diagnosed histologically confirmed cases of invasive epithelial ovarian cancer cases of ovarian cancer among participants aged 18 and 74 in Los Angeles county identified through the USC Cancer Surveillance Program. Cases were primarily white but 308 Hispanic Women and 128 African American women were also included. Controls were selected from residents of LA county and were matched to cases on race/ethnicity and year of birth. Talc exposure was ascertained through in person interviews conducted using standardized questionnaires with a reference date of 12 months prior to diagnosis (or date of interview for controls). Genital talc was reported as no use or less than one year of use, yes use, and use per 5 years of talc.

Among controls the prevalence of talc use ≥ 1 year was 30.4% in non-Hispanic whites, 28.9% in Hispanics and 44.1%. After adjusting for several confounders including race, age group, menopausal status, age at menarche, hormone therapy use, BMI, income, education, life births, tubal ligation, oral contraception, endometriosis, and first-degree family history of ovarian cancer there was a statistically significant increased risk of ovarian cancer associated with genital talc use across all races (OR 1.46, 95% CI: 1.27-1.69), non-Hispanic whites (OR 1.41, 95% CI: 1.21-1.67), and Hispanics (OR 1.77, 95% CI: 1.20-2.62) compared to non-use or less than 1 year of use. The risk was elevated but not statistically significant among African-Americans (OR 1.56, 95% CI: 0.80-3.04) because of low statistical power for the subgroup. Every 5-year use of talc was associated with a statistically significant risk of cancer among the overall population (OR 1.14, 95% CI: 1.09-1.20) and non-Hispanic whites and Hispanics, whereas the excess risk among African-Americans was not statistically significant. The non-response rate for cases (36.8%) and controls was modest. There was no evidence of systematic bias in the ascertainment of exposure as prevalence of various conditions such as endometriosis was consistent with other prior studies.

28. Schildkraut et al. 2016 (52) evaluated African women aged 20-79 years of as part of the African-American Cancer Epidemiology Study. They selected 584 cases of newly diagnosed epithelial ovarian cancer and matched 745 controls to cases on age and region of residence using random digit dialing. Talc exposure was determined through a telephonic interview which included information on baby powder use. Participants were considered regular users if they reported use at least more than 1 time per month for 6 months. Regular users were asked about genital or nongenital use, frequency, duration, and lifetime applications (number of applications per month by number of months used). Since there was a small number of users who reported only genital powder use, they were grouped with genital and non-genital users to "any" genital use. Exposure was examined by frequency of use (less than 30 times per month, daily), duration of use (<20 years, ≥ 20 years) and lifetime number of applications (<3600, ≥ 3600). They also assessed for reporting biases and the effect of stimulant reporting because of the filing of class action lawsuits.

The median duration of body powder use in both cases and controls was 20 years and body powder use were reported among 52.9% of controls. After adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first degree family history of breast or ovarian cancer, and interview year there was a statistically significant increased risk of ovarian cancer with any genital powder use (OR 1.44, 95% CI: 1.11 to 1.86). There was a stronger association for ≥ 20 years of any genital powder exposure compared with <20 years of exposure and the test for trend was significant ($P_{\text{trend}} = 0.002$). Similarly, the ORs for association between daily any genital powder users and EOC were larger in magnitude than never users, and the test for trend was significant ($P_{\text{trend}} < 0.01$) There was also evidence of dose-response for any genital powder for the cumulative number of life-time applications with a higher risk among those with lifetime applications ≥ 3600 ; the test for trend was significant ($P_{\text{trend}} < 0.01$). A stronger association was reported among post-menopausal women who used HRT compared to non-users. There was also an increase associated with non-genital powder exposure (OR 1.31, 95% CI: 0.95-1.79) which was not statistically significant. There was no evidence of statistically significant increased risk with "only" non-genital users and serous ovarian cancer but was statistically significant increased for non-serous ovarian cancer.

Limitations include the assessment of data by self-report. The underreporting of powder use in the abdomen which may reach the genital area may have resulted in a spuriously increased risk among "only" non-genital users or such an effect may be specific to African-American users. Although there was some evidence that there was more reporting of genital powder use

after class action lawsuits in 2014, recall bias alone is insufficient to explain these findings because there was a statistically significantly increased risk both before and after 2014.

29. In 2016, Cramer et al. (54) included 2,041 ovarian cancer cases from Eastern Massachusetts and New Hampshire as part of the Nurses' Health Study and the Ovarian Cancer Association Consortium. Pathology reports were reviewed to confirm diagnosis. The population was primarily white with less than 30 participants who were African Americans, Hispanics, Asians, or other race/ethnicities. Controls were identified through random digit dialing, driver license and town-resident lists and were frequency matched to cases by age and residence. Talc exposure was determined through in person interviews with a reference point 1 year prior to diagnosis or date of interview (for controls). Subjects were asked whether they regularly or monthly applied powder to the genital or rectal area, or on sanitary napkins, tampons or on other non-genital areas. Talc exposure was reported as personal use, potential exposure with no personal use (diaphragm, condoms, partner use), any genital powder use, type of genital powder use (cornstarch, baby powder, other), age of first use, time since exposure ended, frequency of use, years used, months per year of use, and total applications. Lifetime application was assessed by multiplying frequency of application per month with months of exposure. This was divided by 360 to yield talc years which were partitioned into separate quartiles for dose-response analysis. The study adjusted for a variety of confounders, with adjustments for age, study center, study phase, race, BMI, height, weight, parity, breastfeeding, oral contraceptive use, IUD use, ovulatory cycles, endometriosis or painful periods, Jewish ethnicity, family history, personal history of breast cancer, menopausal status, current smoking, ever smoked, asthma, alcohol consumption, and acetaminophen, aspirin or ibuprofen use.

Any genital powder use was reported in 26% of controls. The women who exclusively used cornstarch were considered unexposed. Most talc users began talc exposure around the age of 20. Overall, genital powder use was associated with a statistically significant increased risk of ovarian cancer (OR 1.33, 95% CI: 1.16-1.52) adjusted for age, study center and phase. BMI, smoking and alcohol use did not alter the association by more than 10% suggesting a lack of confounding. Most women reported using Johnson's Baby Powder and Shower to Shower with a trend for increasing risk by talc years. The trend for frequency of use was significant, but the trend for duration of use was flat. The talc ovarian cancer association was largely confined to premenopausal women and post-menopausal women with hormonal therapy. Sensitivity analysis indicated that the risk of misclassification of exposure in controls would have to very high (18%) to nullify the increased risk shown in the study. No data is available

on the extent of misclassification of talc exposure. Although some amount of misclassification is possible in retrospective studies, such a large amount is unlikely as shown by estimates from other analogous exposure-outcome association such as alcohol and breast cancer in the Nurses' Health Study. (114).

IX.III Cohort Studies. I will discuss the cohort studies below. However, it is important to emphasize that none of the cohort studies discussed below were designed to evaluate the association between talc use and ovarian cancer at the time of cohort assembly. In other words, evaluating the association between talc use and ovarian cancer was not the a-priori primary objective of the study but evaluated as a subsequent hypothesis, with its inherent limitations. For example, the NHS cohort was assembled in 1976 but data on talc use was not collected until 1982. (14). In contrast the primary objective of most case-control studies noted above was to evaluate the risk of ovarian cancer associated with talc use.

IX.III.I. In 2000, Gertig et al. (14) reported on an analysis from the U.S. Nurses' Health Study. 121,700 registered nurses were enrolled in the study; 78,630 were included in the cohort study; and 307 cases of ovarian cancer in 11 states. Notably, the Nurses' Health Study was a broad-based study of women's health. Ovarian cancer information was obtained through a questionnaire mailed to married female nurses 30-55 years which were updated every 2 years. Talc exposure was obtained from a survey question which asked "Have you ever commonly used talcum, baby powder, or deodorizing powder a) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or b) to apply on sanitary napkins? No, Yes." Frequency was thus both reported as an "ever, never" metric as well as applications per week but duration of use was not recorded. Information gathered by a questionnaire requesting information on perineal talc use was ascertained only in 1982, and never updated during follow-up. Medical records were obtained for women reporting diagnoses of ovarian cancer or those participants who died (mortality follow up was 98% complete). Histologic subtypes of ovarian cancer were determined from pathology reports and classified as serous (cystadenocarcinoma and papillary adenocarcinoma), mucinous (mucinous papillary adenocarcinoma and adenocarcinoma), endometrioid (clear cell and mixed epithelial), and borderline. Cases of epithelial ovarian cancer (ICD 183.0) confirmed by medical record review or death certificate between 1982-1996 were included in the analyses. Participants who did not respond to the 1982 question on talc use were excluded, as were participants with cancer other than non-melanomatous skin cancer, bilateral oophorectomy, ovarian removal and those with radiation therapy. They included 307 cases of ovarian cancer among 984,212 person-years of follow up (0.03% PYs or 31.2/100,000 PYs). Information on covariates was obtained from the

biennial questionnaire and included oral contraceptive use, tubal ligation, parity, family history (not asked until 1992), smoking and BMI. Age adjusted incidence rates were calculated after adjusting for covariates above, as well as age at menarche, duration of breast feeding, age at menopause. 40.4% (n=31789) reported ever talc use of which 14.5% were ever daily talc users. Women who were talc users and did not have a tubal ligation had no increased risk of epithelial ovarian cancer with talc use- no evidence of interaction. There was an increased risk for histologic subtypes of ovarian cancer with talc use which was not statistically significant (RR 1.09, 95 % CI: 0.86-1.37) after adjusting for age, duration of oral contraceptive use, body mass index, tubal libation history, smoking status, and postmenopausal hormone use. While daily talc use on perineum (RR 1.12, 95% CI: 0.82-1.55) or use less than once/week (RR 1.14, 95% CI: 0.81-1.59) was associated with an excess risk which was not statistically significant, the point estimates for talc use on perineum 1-6 times/week (RR 0.99, 95% CI: 0.67-1.46) and on sanitary napkins (yes/no) (RR 0.89, 95% CI: 0.61-1.28) were lower than 1, and these confidence intervals may not rule out an increased risk. Importantly, there was a statistically significant increased risk for ever talc use for serous invasive cancers (RR 1.40; 95% CI: 1.02–1.91). For women who reported ever daily use, the RR for serous invasive cancer was 1.49 (95% CI: 0.98-2.26). The RRs for ever-users of less than 1 time/week and of 1-6 times/week were 1.29 (95% CI: 0.81-2.04) and 1.49 (95% CI: 0.77-2.11), respectively ($P_{\text{trend}}=0.05$). Women above age 45 in 1982 who reported ever talc use had a higher risk of serous invasive cancer (RR 1.51, 95% CI: 1.07-2.15).

The strengths of the study include the prospective design which reduces the risk of recall bias. The relatively short follow up period may have been unable to determine ovarian cancer. The NHS cohort was not primarily designed to evaluate the association between talc and ovarian cancer. Further, as discussed above, determining “never” use based only on a one-time question near the start of the study (14 years prior to terminating the study in 1996) introduces unidirectional “behavioral change” bias, likely misclassifying some “ever” users who used talc during the study as “never” users; and biased the findings towards the null. The exclusion of prevalent cases of ovarian cancer allows one to determine the influence of exposure on incident ovarian cancer, it also introduces an element of selection bias. Of the initial cohort of 121,700 volunteers, only 78,630 women were enrolled. It is not known whether any (or how many) of the 43,000 excluded women had ovarian cancer, nor whether any (or how many) of any such ovarian cancer volunteers excluded were talc users. They could not determine the intensity of exposure as they had no information on duration of talc exposure, or number of life-time applications or the age at which talc was initiated. The study was not a “new user design” and

used prevalent rather than incident users, and is susceptible to “prevalent user biases.” (15) Prevalent users are “survivors” of the early period of talc use, which can introduce substantial bias if risk varies with time. This may bias findings towards the null due to the “depletion of susceptibles.” They had no data on the intensity of exposure because there was no data on the duration of talc use, or number of life-time applications. The analysis on tubal ligation could not determine whether talc use was initiated after tubal ligation. Any such misclassification of exposure is also likely to be non-differential and bias towards the null.

As a continuation of the Nurses’ Health Study, in 2010, Gates et al. reported on 924 cases of the ovarian cancer as part of Nurses’ Health Study with ovarian cancer confirmed by a gynecologic pathologist review of medical records. (92). They evaluated the findings between risk factors for ovarian cancer and histologic subtypes of ovarian cancer and information on talc exposure was collected through biennial questionnaires. Talc use was reported as either greater than or less than once a week. After adjusting for body mass index activity, past smoking, current smoking, family history of breast or ovarian cancer, age, parity, parous status, breastfeeding, oral contraceptive use, tubal ligation, hysterectomy, age at natural menopause, and estrogen use they reported a non-significantly increased risk of all epithelial ovarian cancer (RR 1.06, 95% CI: 0.89 to 1.28) with genital talc use > once/week compared to < once a week. Although the estimates for the RR were higher for mucinous subtype (RR 1.50, 95% CI 0.84-2.66), there was no evidence of interaction across the subtypes ($P_{\text{heterogeneity}}=0.55$) in this analysis. The strengths and weaknesses of this study are largely like the Gertig analysis of the NHS cohort above, with the additional limitations in the low number of cases (only 29 cases of epithelial ovarian cancer among genital talc users in 108, 870 women).

IX.III.II. In Houghton et al. (17) reported on finding from the Women’s Health Initiative Observational Study (50-79 years at enrollment and post-menopausal). Among the 93,676 volunteers, only 61,576 participants were in the study cohort, and 429 adjudicated incident ovarian cancer (0.7%). Participants completed annual mailed questionnaires. Participants with bilateral oophorectomy, unknown number of ovaries, history of cancer (except non-melanomatous skin cancers were excluded). Perineal powder exposure (rather than specifically talc use) was obtained via self-report at baseline, and not updated during follow-up. Participants were asked whether powder had been used on genital areas, diaphragm or sanitary napkin or pad. If the participant answered affirmatively, there were further questions regarding duration of use where participants indicate use for less than 1 year, 1-4 years, 5-9 years, 10-19 years, or 20

or more years, but frequency of use was not recorded. The area of use was assessed dichotomously, and duration of use was categorized as never, 9 years or less and 10 years or more for analysis. Analysis was conducted for ever perineal powder use (ever use for any of the three categories) and duration for any powder use (maximum duration of any single area of application). Cancer cases were self-reported and confirmed through medical records including pathology reports. Data on covariates for age, race, education, alcohol, metabolic equivalents, smoking, recreational physical activity, oral contraceptive use duration, hormone replacement therapy, family history, age at last birth, BMI, self-reported family history of ovarian cancer were evaluated. They also evaluated reproductive factors such as age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, hysterectomy, irregular cycles, endometriosis. The covariates were obtained at baseline and not updated. The proportional hazards analysis was conducted to examine the risk of ovarian cancer and proportional hazards was tested using Schoenfeld residuals. Participants with other cancers were still considered at risk for ovarian cancer. Covariates were selected for the multivariate analyses, if they had P-values of less than 0.1 during the backward regression until they had a parsimonious model. Additional variables from the literature were also included although they were not statistically significant. They analyzed ever perineal use, perineal use by application area, duration of use and combinations. Test for linear trend was evaluated across duration categories by modeling categories as continuous variables.

The average age of participants was 63.3 years at baseline with 12.4 years of mean follow-up. Most participants were white and were obese. Approximately 52.6% of the population reported ever use of perineal powder. Ever users were more likely to be heavier, used oral contraceptives and/or diaphragms. Perineal use of powder was associated with a 12% excess risk which was not statistically significant ($HR_{adj}, 1.12$, 95% CI: 0.92- 1.36) whereas point estimates for use on sanitary napkins and diaphragms were lower than 1 but could not rule out an excess risk. Duration of perineal, sanitary napkin or diaphragms were not associated with ovarian cancer. Strengths include the prospective design which reduces the risk of recall bias. Limitations includes the lack of information on whether the perineal powder use constituted talc use, and the inability to measure the frequency of exposure. It is possible that the analysis by duration included infrequent long duration users with short term frequent users which may result in bias towards null. Since exposure was not updated during follow-up, some never users who became ever users were misclassified as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer introduced an element of selection bias. Of the initial cohort

of 93,676 volunteers, only 61,576 women were enrolled; 10,622 volunteers who had already developed cancer at baseline were excluded. It is not known whether any (or how many) of these excluded women had ovarian cancer, nor whether any (or how many) were talc users. The inclusion of “prevalent users” rather than “incident users,” leads to depletion of susceptibles and may bias findings towards the null. Data on covariates was not available after baseline resulting in the potential inclusion of participants (e.g., oophorectomy) not at risk of ovarian cancer and resulting bias towards the null. The generalizability of the study findings to younger pre-menopausal women is also unknown as the study findings are limited to older post-menopausal women (average age =63.3 years).

IX.III.III. In 2016 Gonzales et al. (93) examined the relationship between douching, talc use, and ovarian cancer among 50,884 women aged 35-74 years of age (84 % white and 64% post-menopausal) who had never had breast cancer but had a full or half-sister who with breast cancer. They excluded participants with bilateral oophorectomy and ovarian cancer. Among 41,654 participants 154 incident ovarian cancers (n=135 ovarian cancers) were reported (0.3%). Participants completed a telephone interview which included questions about reproductive history (oophorectomies), health and lifestyle and use of personal care products before enrollment, including the use of douching and use of genital talc applied as a powder or spray applied to underwear, sanitary napkin, diaphragm, cervical cap, or vaginal area. The frequency of use was categorized as no use, less than once a month, 1-3 times per month, 1-5 times per week, > 5 times per week, but duration of use was not recorded. As with the WHI and Nurses’ study exposure was only measured at baseline and not updated during follow-up. Updated information on oophorectomy was collected during follow-up and information on cancer cases was collected via annual health update. Data on 37.6% of ovarian cancer cases was available only by self-report and the remainder confirmed by medical record review or death certificate. Cancer cases included tumors of the ovary, fallopian tubes, peritoneum, or of uncertain origin. Those who were BRCA1 or BRCA 1 positive test or those who had a sister with a positive test but had no report of negative test were considered BRCA positive. Cox proportional hazards analysis was conducted until diagnosis of ovarian cancer, oophorectomy, censoring or death. Generalized estimation equations was used to account for familial clustering at baseline. The proportional hazards assumption was evaluated by the goodness of fit test. A joint analysis of talc and douching use was also conducted. The included covariates were patency (yes or no for tubal ligation or hysterectomy), menopausal status, duration of OC use (none, < 2 to <10, 10 or more years), parity (yes/no) race and BMI.

The median duration of follow up was only 6.6 years. The average age was mean 57.8 years for cases. These cases were more likely to have a family history of ovarian cancer and carry a BRCA1 or BRCA2 mutation. More non-cases than cases used oral contraceptives. Talc use was only reported by 12% of cases and 14% of non-cases. Talc users were more likely to have BMI >30 kg/m². Talc use in the last 12 months after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status, and patency, was not associated with a statistically significant increased risk of ovarian cancer (HR 0.73, 95% CI: 0.44-1.20], but could not rule out an excess risk. There was no change in estimates when adjusted for douching. Douching at baseline, more common among talc users, was associated with increased risk of ovarian cancer (HR: 1.8 95% CI: 1.2-2.8).

There were significant limitations to the study. The authors acknowledge that an important limitation of their study was that they collected douching and talc information for the year before the study and did not account for the latency. As with the other two cohort studies, the Sister Study was limited by the issue of selection bias through the exclusion of women who had already developed ovarian cancer (and who could also have been lifetime talc users). Secondly, the Sister Study was vulnerable to behavioral change bias. The bias towards the null of this inaccurate assessment of “ever” user status prospectively, at the start of the study, was compounded by the fact that it was also vulnerable to retrospective inaccuracy, because it was based only on the 12 months preceding baseline. Thus, a participant who had last used talc 13 months before baseline would be categorized as a never-user, as would a participant who started using talc after baseline. Thirdly, the Sister Study’s median follow-up of only 6.6 years is likely insufficient to detect any risk of ovarian cancer which likely takes more than 6.6 years to develop. The study also suffered from the limitations of prevalent user biases. Additionally, exposure was measured as ever/never use in 12 months prior rather than total applications resulting in non-differential misclassification towards the null. Data was only available by self-report on the diagnosis of ovarian cancer for many cases (37.6%) resulting in misclassification of outcome, which was likely non-differential and may bias findings towards the null. The study reported the lowest rate of talc use among the cohort studies (13.8%), further compounding the limited statistical power due to a short duration of follow-up. The generalizability of these findings is also limited as they included women without breast cancer who all had a family history of breast cancer and may be at a higher risk (60%). The missing data were not missing at random and unclear whether analyses were adjusted for missing data. The authors concluded that the study

could not exclude a increased risk despite these findings. The study findings are limited to the predominant cohort of white post-menopausal women who constituted the majority of participants.

IX. IV. Summary of Findings from Epidemiological Studies.

1. The cumulative evidence from these studies demonstrates a statistically significant increased risk of ovarian cancer associated with perineal talc powder use which has been independently replicated by several investigators in different populations, different settings, across different sources using different study designs and time periods. Slight differences in magnitude of risk among these studies may reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time and some variation due to chance. The updated meta-analyses in 2018, which have included all the studies, reported a statistically significant increased risk of perineal talc use and ovarian cancer, (41, 42), with little evidence of statistical heterogeneity or publication bias. The case-control studies provided 13,421 cases compared to 890 cases in the cohort studies. (42). Most case-control studies demonstrate an increased risk of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors.

2. Meta-analysis which evaluate the association between perineal talc use and ovarian cancer have consistently shown an increased risk of ovarian cancer, (39, 41, 42, 73, 79), including pooled analysis using individual participant data. (10). My conclusions about the causal increase in the risk of ovarian cancer associated with talc exposure are heavily weighted by recent cumulative meta-analysis published in 2018, (41, 42). These meta-analyses provide the most comprehensive evidence base given the size of the study database and their methodologic superiority as assessed by the AMSTAR rating above. (Table 1). Also, importantly, there is no meta-analysis which has reported a statistically significant decreased risk of ovarian cancer with talc.

3. The only case-control study in which point estimates are below one was limited by the poor choice of controls and very high non-response rates. Despite these limitations it could not rule out a 21% increased risk of ovarian cancer associated with talc use which is not inconsistent with other studies. (86). Although the exposure rate to talc in the case-control studies has been variable in the control group from 5%-45%, this reflects the varying practices in the use of talc rather than the lack of an increased risk of ovarian cancer with talc use.

4. Although all studies are at potential risk of outcome misclassification, most of the studies used histologically verification for the diagnosis of ovarian cancer. Any such potential

misclassification of outcomes is likely to be non-differential and would have biased the findings towards the null.

5. There is no reason to believe, from the studies, that ovarian cancer would result in talc use, so the temporality of the association is established.

6. Case-control studies are susceptible to recall bias particularly when data on exposure are self-reported. However, several studies have included these questions on talc exposure as a part of larger questionnaires on other risk factors minimizing the possibility of recall bias. Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures. Further, recall bias is equally likely to affect other histologic types of ovarian (and endometrial) cancer but here the increased risk was limited to only epithelial ovarian cancer in most studies. Finally, the findings that only perineal talc use was associated with ovarian cancer but not with non-genital talc use argues against recall bias alone as a potential explanation of these findings.

7. Confounding is one potential explanation for these findings. However, several case-control studies adjusted for major confounders including the more recent case-control studies. (54). Although residual confounding is always possible in an observational study, studies that have reported adjusted and non-adjusted findings have reported similar results minimizing the impact of residual confounding. (41). Although there are some risk factors for ovarian cancer (e.g., genetic risk factors, family history, obesity and reproductive history), for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. To invalidate the statistically significant findings of an increased risk of ovarian cancer from the studies, one would have to postulate a degree of selection, recall bias and confounding pervasive across different time periods, different populations which is highly implausible.

8. Case-control studies are also at risk of selection bias which may introduce bias in both directions. As opposed to hospital-based controls, which may be less susceptible to selection bias, the population-based case-control studies have consistently showed a higher estimate of increased risk of ovarian cancer associated with talc use.

9. Reverse causality, where the diagnosis of ovarian cancer results in perineal use of talc, may be one possible explanation of the nonsignificantly increased risk in the group exposed to perineal talc. However, this is also likely minimal in the case of ovarian cancer in which most

cases present at advanced stages with abdominal bloating, and vaginal symptoms only occur in a small minority of cases.

10. One of the cohort studies reported an increased risk with perineal talc exposure and serous invasive cancer (14). The pooled results from all three cohort studies, reported an excess risk of ovarian cancer, (42) which failed to reach statistical significance because of several limitations. The duration of follow up was limited resulting in low number of events and inadequate statistical powder. The only cohort study which reported an inverse association between perineal talc use and ovarian cancer included several other cancers beyond the ovary (such as peritoneum, endometrial) (93), which may have diluted an increased risk. It had a very short duration of median follow up of approximately 6.6 years which is insufficient to ascertain the development of ovarian cancer. Since talc induced carcinogenesis occurs via a foreign body mechanism, the latency period required to demonstrate such an effect is long. Despite these limitations, the upper bounds of the confidence intervals exceeded one and could not rule out an increased risk of ovarian cancer with perineal talc use. The cohort studies were at risk of significant other biases. Exposure was measured at baseline and not updated during follow-up (14, 17), which may have misclassified those participants at baseline who were never users but used talc during the study as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer (some of whom may have been exposed to talc) may also bias their findings. (14, 17) The cohort studies were also susceptible to “depletion of susceptibles” biasing their findings towards the null. None of the cohort studies were primarily designed to study the association between genital talc use and ovarian cancer as their primary objective. Despite these limitations, the meta-analysis of cohort studies demonstrated a statistically significant increased risk of serous invasive ovarian cancer.

11. Ascertaining *dose response* relationship with talc and ovarian cancer is difficult because of the challenges in quantifying talcum powder use usually collected by self-reported data (frequency, amount and duration), timing and patterns of use (e.g. douching), and other individual factors (e.g. co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. The dose response depends on both the amount of talc exposure, the frequency of talc uses and the duration. It is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an “application of talc.” Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open, the age of initiation of talc use since the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (79). The presence of other risk factors

such as post-menopausal status, cancers other than invasive serous ovarian cancer may make it difficult to ascertain a dose-response relationship among older post-menopausal. The lack of statistical trend (58, 60) in some earlier studies may reflect some of these challenges as well the lack of a monotonic dose response effect. The exposure-response data need to be interpreted in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer in susceptible individuals through accelerating the redox state in epithelial ovarian cancer cells. (49). Thus, an assessment of the gradient through a monotonic dose-response curve may not provide a complete picture of the biological gradient. It unclear why nature would mandate an increasing mono-tonic dose-response mechanism for causation, and some have argued that among Bradford-Hill viewpoints it is difficult to know how dose-response should be modelled. (50). Cumulative lifetime exposure may be a more appropriate measurement of exposure given the inflammatory mechanisms by which talc induces the development of ovarian cancer. It is important to recall that if the carcinogenicity of talc induced ovarian cancer most likely resembles that of asbestos induced mesothelioma (with which it shares histologic similarities), asbestos induced mesothelioma does not have a dose-response relationship. In the case of asbestos induced mesothelioma, latency may be more important whereas in the case of talc induced ovarian cancer induced by inflammation latency may be of lesser importance.

12. Despite these challenges, several studies have shown evidence of dose-response as measured by an increased risk with increased frequency (51-55) or increased duration, (52, 54) or combination of frequency and duration of exposure. (48, 54). Some studies show a exposure-response trend, (54) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). In the individual participant data meta-analysis a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis, but no significant trend was seen when analyses were restricted to ever users. (10) Importantly, the most recent meta-analysis reported an evidence of dose-response with risk being higher among those with >3600 applications of talc compared to participants with <3600 applications. (42) Both of these categories of exposure were associated with an increased risk of ovarian cancer. None of the cohort studies were able to conduct meaningful dose-response analysis because they did not collect data either on duration, (14, 93) or frequency of exposure. (17).

X. BIOLOGICAL MECHANISMS OF TALCUM POWDER INDUCED OVARIAN CANCER.

Although not an absolute requirement for determination of causation there are multiple well-established biological and molecular mechanisms by which talcum powder products induce ovarian cancer. The key routes of exposure and biological mechanisms are noted below.

X.I. Retrograde Migration of Talc Particles. Genital talc can migrate up to the fallopian tubes and ovaries and talc particles have been detected within the ovaries of women who report perineal talc use. Heller et al. detected talc in the ovaries of 24 women undergoing incidental oophorectomy demonstrating that it can reach the upper genital tract (64) although the fact that talc particle counts were unrelated to reported levels of perineal talc exposure reflects the challenges in measuring exposure to talc. Talc has been found deeply embedded within ovarian tumors, (65) and subsequent studies have confirmed that these are not due to contamination. (94). Talc has also been demonstrated in pelvic lymph nodes of women with perineal talc exposure.(66). Supportive evidence of migration comes from studies showing retrograde migration of additional particles such as starch after gynecological examination, (68) findings of a decreased risk of ovarian cancer with tubal ligation and hysterectomy in case-control studies, (87) and meta-analysis, (115) which may minimize exposure to inflammatory particles. Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of “measurable quantities of talc’ in monkey models, (67) the timing and techniques of assessment and intraspecies differences could not rule out migration of talc particles. The FDA response to Citizen’s Petition 2014 concluded the “*potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable*’. Johnson & Johnson and IMERYS documents also acknowledge migration. In one document it was stated, “A review of the literature suggests that it is biologically plausible for talc particles to migrate from the vagina to the peritoneal cavity and ovaries following perineal application.” (63, 116).

X.II. Inhalation of Perineal Talcum Powder. Inhalation of talcum powder is another potential route of exposure that is biologically plausible and can cause inhaled fibrous talc (and asbestos) fibers to reach the ovary and thus increase the risk of ovarian cancer in women using these products. Approximately 50 percent of talc particles in commercially available talcum powder are less than 10 microns in size, (117) which have the potential for inhalation and reach the alveolar regions of the respiratory tract. (118) Asbestos fibers can pass from the alveoli to the

lung interstitium, from which they can travel via the lymphatic system to the bloodstream and other organs including ovaries. (119, 120) Inhaled fibrous talc shares extensive physical and chemical similarities with asbestos, and inhaled fibrous talc generated from perineal application may also reach the ovaries by inhalation. This mechanism was confirmed in a September 2017 study, "Below the Waist Application of Johnson & Johnson Baby Powder," Longo, et al. showed that normal application of Johnson's Baby Powder can produce airborne asbestos and talc fibers which could be inhaled. (70).

X.III. Talcum Powder Induced Inflammation and Alteration of Redox Potential. Inflammation has long been understood to be an important mechanism underlying the development of ovarian cancer. (61). Inflammation may underlie ovulatory events because an inflammatory reaction is induced during the process of ovulation. Risk factors for ovarian cancer include endometriosis (i.e., ectopic implantation of uterine lining tissue) and pelvic inflammatory diseases (PID). (121). PID was associated with an increased risk of borderline ovarian tumors, particularly among women who had had multiple episodes of pelvic inflammatory disease in a meta-analysis. (122). Consistent with the inflammatory mechanism for ovarian cancer, a prospective nested case-control study from the Prostate, Lung, Colorectal and Ovarian Cancer has also shown that global markers of inflammation such as C-reactive protein, Interleukin L-1 α , Interleukin-8 and Tumor Necrosis Factor- α are associated with a significantly increased in the risk of ovarian cancer. (123). Supportive evidence for the role of inflammation also comes from a meta-analysis showing a decreased risk of ovarian cancer with tubal ligation and hysterectomy. (115). Studies have demonstrated increased risk of ovarian cancer with talcum powder use, and increased risk of ovarian cancer with endometriosis. (87). This risk is 3-fold higher among women exposed to talc who have endometriosis. (48).

Oxidative stress in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays a role in the pathogenesis, neo-angiogenesis (formation of new vessels) and the dissemination of both early and late stage epithelial ovarian cancer. (124, 125). Epithelial ovarian cancer cells manifest a persistent pro-oxidant state characterized by upregulation of certain key oxidant and downregulation of key antioxidant enzymes, (125) and the presence of oxidative stress triggers cancer cells to favor anaerobic metabolism. Oxidative stress induces phenotypic modification of tumor cells by altering cross-talk between tumor cells and surrounding stroma. Talc can alter this redox state and cause a marked increase in mRNA levels of the prooxidant enzymes, iNOS (nitrous oxide) and MPO (myeloperoxidase) in talc treated ovarian cancer cells as compared to control as early as 24 hours in all doses, (49) as well as a marked decrease in the

mRNA levels of the antioxidant enzymes catalase CAT, glutathione peroxidase (GPX), and superoxide dismutase (SOD3) providing a mechanism by which talcum powder products can induce the development of ovarian cancer.

Cancer antigen [CA-125] a tumor marker secreted by the epithelial cell for monitoring recurrence after treatment of ovarian cancer, was elevated when both normal ovarian cell lines [1.7 +/- 0.5-fold] and ovarian cancer cell lines [1.4±0.5 and 4.4±0.5-fold increase in OV90 and TOV-21G EOC cell lines] were exposed to talc, providing another molecular mechanism by which talc can increase the risk of ovarian cancer. (106).

Talc has been shown to increase proliferation, induce neoplastic transformation and increase ROS generation time-dependently in the normal human epithelial and granulosa ovarian cells and dose-dependently in the polymorphonuclear neutrophils. (71). In studies of human mesothelial cells, both nonfibrous talc and asbestos have shown evidence of genotoxicity. (109) Some have suggested that perineal talc use may also increase risk of ovarian cancer by the induction of anti-MUC1(monoclonal antibodies) possibly via heat-shock protein, (72) although the data are not definitive. (101).

X.IV. Carcinogenicity in Animal Studies. Among animal studies a study among rats demonstrated the development of papillary changes after intrabursal injection of talc. Such papillary changes may be precursors of serous papilloma precursors of epithelial cancers. (107). Another 2-year inhalation study with cosmetic grade talc in rats and mice showed evidence of carcinogenic activity in male (an increased incidence of pheochromocytomas of the adrenal gland) and female (increased incidences of alveolar/bronchiolar adenomas) rats and carcinomas of the lung and pheochromocytomas of the adrenal gland. (108). There was no evidence of carcinogenicity in mice. However, limitations of this study include the lack of a suitable control (e.g. titanium dioxide), alternative explanations of these findings via particle overload, (127) and the fact that ovulatory patterns in rats are not fully applicable to humans.

X.V. Presence of Asbestos and other carcinogens in Talcum powder products. In assessing the biological plausibility of talcum powder products as a cause of ovarian cancer, it is important to consider the constituents of talcum powder products including whether it contains known or suspected carcinogens. The presence of asbestos in talcum powder products can and does provide a plausible biological explanation of the development of ovarian cancer. (36, 37).

Occupational exposure to asbestos is a well-established causal agent for the development of pleural and peritoneal mesothelioma, larynx and ovarian cancer. (36, 127). Talc and asbestos also share chemical similarities. The carcinogenicity of asbestos relies on shape of particles with long thin fibers-such as those occurring in crocidolite asbestos being particularly carcinogenic. Although talc consists primarily of platy talc, it may also contain fibrous talc or other asbestiform minerals. Epithelial ovarian cancer, one most closely associated with talc, histologically most closely resembles mesothelioma providing further evidence of biological mechanisms. As Huncharek notes in their meta-analysis of ovarian cancer associated with talc dusted diaphragm meta-analysis on page 427 "*If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogen effect as it contains a known carcinogen.*" (13). In addition talcum products contain fibrous talc, heavy metals and fragrance ingredients which are known or suspected carcinogens. (26, 33, 35, 36). Like the presence of Asbestos Fibers, the presence of these known or suspected carcinogens provide a plausible biologic explanation for the increased risk seen in the epidemiologic studies.

XI. ASSESSMENT OF CARCINOGENECITY OF TALC BY THE IARC IN 2006.

The International Agency for Research on Cancer (IARC) expert panel evaluates the carcinogenicity of various products using the following criterion after review of animal studies, experimental studies and epidemiological data. (128). The data is examined to determine whether there is *sufficient evidence, limited evidence, inadequate evidence, or evidence suggesting lack of carcinogenicity* for both cancer in humans and animals, respectively. The mechanistic and other relevant data are examined to *identify established and likely mechanisms and determines whether each mechanism could operate in humans*. The agents are then classified into several groups. Group 1 are agents *carcinogenic* to humans (e.g., asbestos,) (37), Group 2A are agents *probably* carcinogenic to humans, Group 2B *possibly* carcinogenic to humans, Group 3 agents which are *unclassifiable* and Group 4 agents which are *probably not carcinogenic* to humans.

In 2006 IARC concluded that perineal use of talc not containing asbestos or asbestiform fibers was possibly carcinogenic to humans (129) based on *limited evidence in humans for the carcinogenicity of perineal use of talc based body powder and the limited evidence in experimental animals for the carcinogenicity of talc* (93) (Group 2B-b). (38). Although a positive association has been observed between exposure to the agent and cancer for which causal interpretation is considered by the Working Group to be credible, but chance, bias, or confounding could not be ruled out

with reasonable confidence. For purposes of their evaluation, IARC considered 19 case-control studies and 1 cohort study. (14). The Working Group concluded that 8 of the more informative case-control studies (as well as most of the less informative ones) showed a consistent excess risk in the order of 30-60%. The cohort studies neither supported or refuted the evidence from case-control studies.

The IARC assessment was carried under the assumption that talcum powder products did not contain asbestos based on the published findings at the time- an assumption that is not supported by current data. In such a case, talcum powder products would be unequivocally classified as a Group 1 carcinogen like asbestos. Importantly, even absent a finding of asbestos in talcum powder products, the consistent cumulative evidence of peritoneal use of talcum powder products demonstrates an increased risk of ovarian cancer. Several *new systematic reviews based on recently published studies have further added to the accumulating evidence on an increased risk of ovarian cancer with talc use.* (10, 41, 42). *There is now further evidence of exposure response relationships, with measured by an increased risk with increased duration (52, 54) or combination of frequency and duration (48) and the most updated meta-analysis show evidence of duration dose and responsiveness.* (42). Finally, in addition to the epidemiologic evidence there is evidence from toxicology , molecular biology and other mechanistic data which supports my opinions .

XII. COSMETIC EXPERT REVIEW PANEL REPORT.

For the sake of completeness I also reviewed a report on the safety of cosmetic talc by an industry sponsored panel. (130). The panel was primarily composed of dermatologists, with limited expertise in epidemiology and carcinogenicity. The review was carried out under the flawed assumption that cosmetic-grade talc must contain no detectable fibrous, asbestos minerals and thus limited its assessment to animal and clinical studies on talc that did not contain asbestos, and erroneously concluded that there was no evidence of talc migration. As a result of these serious methodologic shortcomings and funding biases it arrived at its erroneous conclusions that talc was safe for use in cosmetics. (130) As discussed above, the findings of this panel have been superseded by findings from several new epidemiological studies, mechanistic studies and systematic reviews which have further added to the accumulating evidence on an increased risk of ovarian cancer with talcum powder product use.

XIII. ASSESSMENT OF CAUSALITY.

While talc is clearly associated with development of ovarian cancer, we must assess whether the observed association leads to an inference about causation. In 1965, in the President's Address to the newly-established Section of Occupational Medicine of the Royal Society of Medicine, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics at the University of London, attempted to encapsulate the aspects of a causal relationship, as it was understood at the time. (1). As he described them, they were: 1. strength of association, 2. consistency, 3. specificity, 4. temporality, 5. biological gradient, 6. plausibility, 7. coherence, 8. experiment, and 9. analogy. As Professor Hill explained, no aspect alone is either necessary or sufficient: "What I do not believe . . . is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence . . . and none can be required as the *sine qua non*." Further, according to Professor Bradford Hill, these are not the only aspects of causation, but they are informative. It must also always be remembered, as highlighted in a recent statement by the American Statistical Association, that a lack of statistical significance does not imply lack of clinical significance (18) – a point also highlighted by Bradford Hill, who noted that while statistical tests can remind us of the role of chance, "*No formal tests of significance can answer those questions.*"

With respect to the analysis at issue, that is, the association between talcum powder products and ovarian cancer—the results are not only statistically significant, but, as described above, have been replicated by several independent authors in multiple studies across a range of study designs. The cumulative body of evidence was appraised using the Bradford Hill viewpoints. In this regard, and as described in this report, I put significant weight on the Strength, Consistency, Temporality, Biologic Plausibility, and coherence factors and, to a lesser extent, Gradient (Dose-Response) and Analogy data to support my opinion that Talcum Powder Products can cause ovarian cancer. For the reasons stated below, I do not weigh heavily the Experiment and Specificity data in light of the totality of the evidence supporting a causal inference. My assessment is described below.

1. Strength of Association. This aspect of a causal relationship refers to the degree or magnitude of effect to which the exposure is associated with the outcome. (1). According to Bradford Hill, the more likely the exposure is associated with the outcomes, the more likely is it to be causal. As summarized in the meta-analysis in section above, I conclude that the association of talc with

ovarian cancer shows an approximate 30-60% relative increase in the risk of ovarian cancer, after adjustment for multiple confounders of the talc and ovarian cancer relationship. (10, 42). The strength of the association, replicated in multiple studies, provides evidence in support of a causal association. There are several noteworthy examples of well-established causal relationships (e.g. second hand smoking and lung cancer), (131) where the strength of the association is in the order of 20-40%. Such causal associations can have significant effects on the population if a large segment of the population is exposed, as in the case of air pollutants and myocardial infarction, which are significantly associated with an increase in MI risk with small relative risk (carbon monoxide: 1.048; 95% CI, 1.026-1.070; nitrogen dioxide: 1.011; 95% CI, 1.006-1.016; sulfur dioxide: 1.010; 95% CI, 1.003-1.017; PM₁₀: 1.006; 95% CI, 1.002-1.009; and PM_{2.5}: 1.025; 95% CI, 1.015-1.036) but a large population burden because of the large percentage of the population that is exposed. (47). Similarly, 75-100 mg of daily Aspirin has been shown to reduce the risk of cardiovascular events among those weighing 50-69 kg by 25 % [HR 0.75, 95% CI, 0.65-0.5] (132) in an individual participant data meta-analysis of randomized controlled trials. An increment of one serving a day of fruit and vegetables reduced all-cause mortality by 5% (HR 0.95 95% CI: 0.92 - 0.98) in a meta-analysis of cohort studies. (133). As discussed below, I place significant weight on the fact that studies demonstrate a strong association between talcum powder use and ovarian cancer and show consistency of the data.

2. Consistency. This viewpoint assesses whether the finding is repeated in different settings, place and time. (1). As shown in detail above, the direction and strength of association of talc and ovarian cancer is generally consistent across studies, including observational studies of various designs and their meta-analysis, and observational studies. These studies have been conducted in different clinical settings across the world, with different duration of follow up and the cumulative evidence has consistently shown a significantly increased risk of ovarian cancer with the use of talcum powder products. As expected, there are slight differences in the point estimates which reflect differences in study population with nearly all point estimates showing a direction of increased risk of ovarian cancer. The confidence intervals, however, across study designs overlap, indicating consistent results. I place significant weight on the fact that the consistency and strength of the association found in multiple independent studies demonstrates that the association is causative.

3. Specificity. This viewpoint considers whether the outcome of the disease appears to be specific to the exposure, (1) although since the original publication of the Bradford Hill we know

in most cases, absolute specificity for an exposure outcome association is not generally possible for many diseases, particularly cancer, and not required to provide proof of causation. Even the well-established, causal relationship between cigarette smoking and lung cancer or heart disease is not characterized by specificity. Genetic factors may also play a role in the occurrence of ovarian cancer. As discussed above, the occurrence of ovarian cancer is consistently higher among talcum powder users compared to non-users, even after adjusting for several confounders. I placed less weight on absolute specificity of the association between talcum powder exposure and ovarian cancer given the multi-causal nature of the outcome, particularly in light of the strength and consistency of association factors.

4. Temporality. The temporality viewpoint assesses whether the exposure always predates the development of disease. (1). In each of the epidemiologic studies noted above, talc exposure occurred before the diagnosis of ovarian cancer. Although some have argued that some of the symptoms of ovarian cancer (vaginal bleeding, irritation) may lead to talcum powder use, since most ovarian cancers present with abdominal bloating and advanced stages of the disease it is difficult to attribute how development of ovarian cancer would lead to talc use (e.g., reverse causality). I placed significant weight that the exposure to talc preceded the development of ovarian cancer in the studies above.

5. Biological Gradient. This viewpoint assesses whether there is a biological gradient or dose-response effect, (1) recognizing that presence of dose-response is not an absolute requirement for causation. In order to determine dose-response, it is necessary first to determine dose. While the presence of a dose-response relationship supports a causal link, the absence of such a relationship does not preclude a causal association. The causal relationship between asbestos and mesothelioma, which most closely resembles the current scenario is not dose-dependent. Assessing dose-response is challenging in the context of perineal talc use for several reasons: first, unlike, say, birth-control pills, the amount of talc powder product use is not fixed, nor is the number of uses per time (day, week, or month). At a minimum, to assess total dose, it is necessary to acquire information about both duration and frequency. Ascertaining a dose-response relationship with talc and ovarian cancer is particularly challenging given that the risk of ovarian cancer may vary with age, premenopausal and post-menopausal status and the presence of other risk factors. The dose-response depends on both the amount of talc exposure, the frequency of talc uses and the duration. The presence of other risk factors such as post-menopausal status, cancers other than invasive serous ovarian cancer and the “depletion of

susceptibles” over time may make it difficult to ascertain a dose-response relationship. Several studies show evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 54). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis show evidence of duration dose and responsiveness, (42) with risk being higher among those with >3600 applications of talc compared to participants with < 3600 applications, although with overlapping confidence intervals. (42). Based on the above limitations with study design to ascertain dose effect, specificity of dosing of talc and the possibility of threshold effect, I find biological gradient less compelling, but still compelling of my causation analysis than the other Bradford Hill overviews as referenced above.

6. Plausibility. Although this is not a requirement for causation, an association that is biologically plausible is more likely to be causal. (1). While this viewpoint only requires biological mechanism to be *plausible*, which is necessarily limited to the state of biological knowledge at the time of assessment, evidence from the literature described in detail in the section in biological mechanisms shows multiple routes of exposure, multiple pathways and multiple mechanism by which talc can cause ovarian cancer. **Section X** demonstrates how talcum powder products can migrate to the ovaries, induce inflammation, alter redox potential resulting in a pro-oxidant state, (49) and act as a mutagen. (109). As a results of the significant body of evidence that has accumulated on biological mechanisms, I place significant weight on the fact biological plausibility provides evidence in support of the causal role of talc in the development of ovarian cancer and there is a highly biological plausible mechanism here for carcinogenicity which supports my opinion.

7. Coherence. This viewpoint assesses whether the cause-and-effect interpretation of data conflicts with the generally known facts of the natural history and biology of the disease. (1). The evidence on the risk of ovarian cancer with talcum powder exposure is consistent with the nature of the disease. Multiple studies suggest that talcum powder products have biological effects which plausibly explain the occurrence of ovarian cancer. Given the biological mechanisms related to inflammation described above, this mechanism and causal association itself fit easily within the current framework of scientific knowledge about the development of

ovarian cancer mediated by inflammation. I placed a significant weight on the coherence of findings in support of the causal role of talc in the development of ovarian cancer.

8. Experiment. Occasionally, in making a causation assessment, it is possible to appeal to experimental, or semi-experimental, evidence. The definitive experimental evidence would be a placebo controlled randomized trial among patients who are assigned to use talc and others who do not use talc in which the outcome of incident ovarian cancer would be actively ascertained. However, such evidence does not exist and would not be ethical nor feasible with a rare outcome such as ovarian cancer with an incidence of 11.4/100, 000 person-years noted above. While there is no randomized controlled trial here, that is common when dealing with a suspected cancer risk. For instance, there is no randomized controlled trial which supports the causal role of smoking in lung cancer. Such a trial to provide absolute proof of harm, which ignores the body of evidence that has accumulated and places patients at risk for developing ovarian cancer raises significant ethical concerns when data from robust observational studies and their meta-analysis have consistently shown an increased risk of ovarian cancer. In the absence of experimental evidence, this overview is weighted as less important than the other more important viewpoints noted above.

9. Analogy. Asbestos has been shown to cause ovarian cancer which offers an appropriate analogy, (40) but this viewpoint was considered less significant than other viewpoints noted above.

XIV. CONCLUSIONS.

Based on my background, training and education as a physician and epidemiologist, review and analysis of the totality of the evidence, using the weight of evidence analysis, including considering and weighting the Hill viewpoints, as described in this report, it is my opinion stated to a reasonable degree of scientific and medical certainty that peritoneal use of talcum powder products can cause ovarian cancer.

Signed this 16th day of November 2018

A handwritten signature in cursive script, appearing to read "Sonal Singh", followed by a horizontal line.

Sonal Singh, MD, MPH

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Table 1. AMSTAR (Assessing the Methodologic Quality of Systematic Reviews) Rating of Systematic Reviews and/or Meta-analysis of Genital Talc use and Ovarian Cancer									
Criterion	Harlow et al 1992 ¹	Gross and Berg et al 1995 ²	Cramer et al 1999 ³	Huncharek et al 2003 ⁴	Langseth et al 2007 ⁵	Terry et al 2013 # ⁶	Berge et al 2018 ⁷	Penninkilampi and Eslick 2018. ⁸	Huncharek et al 2007 ^{9*}
<i>A priori design</i>	UA	Y	N	UA	UA	Y	Y	Y	UA
<i>Duplicate study selection & extraction</i>	N	N	N	Y	N	NA	Y	Y	Y
<i>Comprehensive search</i>	N	N	N	UA	N	NA	Y	Y	N
<i>Status of publication used as criterion</i>	UA	N	UA	Y	UA	NA	Y	N	Y
<i>List of included & excluded studies</i>	N	N	N	N	N	Y	Y	Y	N
<i>Characteristics of studies provided</i>	N	Y	N	N	N	Y	Y	Y	Y
<i>Scientific quality of studies addressed</i>	N	UA	N	N	Y	Y	Y	Y	N
<i>Scientific quality of studies used in formulating conclusions</i>	N	Y	UA	N	Y	Y	Y	Y	N
<i>Methods of combining studies appropriate</i>	N	Y	Y	Y	Y	Y	Y	Y	N
<i>Likelihood of publication bias addressed</i>	N	N	N	N	N	NA	Y	Y	N
<i>Conflict of interest included</i>	Y	Y	Y	UA@	Y	Y	Y	Y	UA@

*Meta-analysis by Huncharek et al in 2007 et al evaluated only talc on contraceptive diaphragms

Terry et al 2013 conducted an individual participant data pooled analysis so several items for systematic review NA

@ Incomplete financial disclosures of role of sponsor in meta-analysis

Y= Yes N= No; NA= Not applicable; UA : Unable to answer

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Additional Materials and Data Considered

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Other Materials

1. WCD000254-WCD000255
2. IMERYS210136-IMERYS210137
3. IMERYS241994-IMERYS242004
4. IMERYS242050
5. IMERYS322241-IMERYS322242

6. IMERY5422289- IMERY5422290
7. JNJ000087166-JNJ000087230
8. JNJ000251888-JNJ000251890
9. JNJ000261010-JNJ000261027
10. JNJ000460665-JNJ000460673
11. JNJ000526231-JNJ000526676
12. JNJAZ55_000000577-JNJAZ55_000000596
13. JNJAZ55_000003357
14. JNJAZ55_000012423-JNJAZ55_000012430
15. JNJI4T5_000004099-JNJI4T5_000004100
16. JNJI4T5_000006431-JNJI4T5_000006432
17. JNJMX68_000004996-JNJMX68_000005044
18. JNJNL61_000001534-JNJNL61_000001535
19. JNJNL61_000014431-JNJNL61_000014437
20. JNJNL61_000020359
21. JNJNL61_000052427
22. JNJNL61_000061857
23. JNJNL61_000063473
24. John Hopkins, Trial Testimony, *Berg v. Johnson & Johnson* 2013
25. Deposition Transcript & Exhibits – John Hopkins, Aug. 16 & 17, 2018, Oct. 26, 2018, Nov. 5, 2018
26. Deposition Transcript & Exhibits – Joshua Muscat, Sept. 25, 2018
27. Deposition Transcript & Exhibits – Julie Pier, Sept. 12 & 13, 2018
28. Deposition Transcripts - Linda Loretz, Oct. 2, 2018
29. Deposition Exhibits for Linda Loretz - Exh. 106, 107, 108, Oct. 2, 2018
30. Deposition Transcript of Alice Blount, Apr. 13, 2018
31. Educational report of Thomas Dydek
32. Expert report of Jack Siemiatycki.
33. Expert report of Laura Plunket (Oules).
34. Fair warning TalcDoc 15.
35. Fair warning TalcDoc 5- Exhibit 113 (JNJNL91_000022019).
36. Letter from Cancer Prevention Coalition to FDA re: Citizen's Petition seeking carcinogenic labeling on all cosmetic talc products, Nov. 17, 1994.
37. Letter from Cancer Prevention Coalition to FDA re: Citizen's Petition seeking a cancer warning on cosmetic talc products, May 13, 2008.
38. Letter from Personal Care Products Council to FDA re: Comments on Citizen's Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products, July 21, 2009.
39. Transcripts of CIR meeting (Unpublished)

40. Rothman, Pastides, Samet. Interpretation of epidemiologic studies of talc and ovarian cancer. 2000.
41. Zuckerman D, D Shapiro. Talcum Powder and Ovarian Cancer, National Center for Health Research, May 7, 2018 <http://www.center4research.org/talcum-powder-ovarian-cancer/>

EXHIBIT A

Sonal Singh, MD MPH
55 Lake Ave North
Worcester, MA 01655-0002 USA
Tel: 774 442 6611.
Sonal.Singh@umassmemorial.org

Education

MPH, Bloomberg School of Public Health, Johns Hopkins University
Baltimore, MD 6/2005 to 5/2008

Internal Medicine Residency, Unity Health System, affiliate University of Rochester
Sch of Medicine and Dentistry, Rochester, NY 7/2002 to 6/2005

MD, Patna Medical College, Patna, India 12/91 to 05/1999

Academic Appointments

Associate Professor, Department of Family Medicine & Comm Health 10/2016 to date
Department of Medicine, University of Massachusetts Medical School

Assistant Professor, Dept of Medicine, Johns Hopkins Univ SOM 7/2009 to 9/2016

Assistant Professor, Center for Public Health and Human Rights
Bloomberg School of Public Health, JHU (joint) 7/2009 to 9/2016

Assistant Professor, Department of Medicine, Wake Forest University 7/2007 to 6/2009

Instructor, Department of Medicine, Wake Forest University 7/2005 to 06/2007

Employment History

Associate Professor, Department of Fam Medicine & Comm Hlth 10/2016-present
Meyers Primary Care Institute & Department of Medicine (Joint)
University of Massachusetts Medical School
Role: Clinician- Investigator

Associate Professor, Department of Quantitative Health Sciences 10/2018-present
University of Massachusetts Medical School
Role: Clinician- Investigator

Assistant Professor, Dept of Medicine, Johns Hopkins University. 7/2009 to 9/2016
Role: Clinician- Investigator

Assistant Professor, Department of Medicine, Wake Forest University 7/2007 to 6/2009
Role: Clinician- Educator

Instructor, Department of Medicine, Wake Forest University 7/2005 to 6/2007

Sonal Singh M.D., M.P.H

Role: Clinician- Educator

Residency (Medicine) Unity Healthy System, affiliate of the University of Rochester, Rochester,
NY 7/2002 to 6/2005

Role: PGY 1, PGYII and PGY III Internal Medicine Resident

Research Associate, Clinical Pharmacology, Ohio State University 3/2001 to 6/2002

Role: Research assistant in clinical trials

Voluntary Research Associate, Clinical Pharmacology, Ohio State University 8/2000 to 2/2001

Role: Research assistant in clinical trials

USMLE STEP 1, II, III and Clinical Skills Exam Preparation 2/2000 to 7/2000

Role; Medical student

Resident, Medicine, Patna Medical College, Patna, Bihar, India 2/1998 to 1/2000

Role: Junior Resident in Medicine

Compulsory rotatory internship, Patna Medical College, Patna, India 12/97 to 12/98

Role: Fulfilling requirements for completion of medical degree in India

Certification and Licensure

Diplomate, American Board of Internal Medicine 8/2005-12/25

Massachusetts Board of Physicians 8/2016-8/2019

Physicians and Surgeons of Maryland (Inactive) 2009-2017

North Carolina Medical Board (Inactive) 2005 to 2009

Professional Memberships and Activities

Massachusetts Medical Society 2017-current

American College of Physicians 2003-2019

International Society of Pharmacoepidemiology 2011-current

Society of General Internal Medicine 2003 to 2016

International Society of Pharmacoeconomic Outcomes Research 2016 to 2017

Academy Health 2013

Global Health Council 2006 to 2010

Honors and Awards

Finalist W. Leigh Thompson Excellence in Research: Faculty Award, JHU	2016
Visiting Professor, Department of Medicine, Univ of Alabama	2013
3 rd Best Abstract (trainee) 29 th ICPE Montreal, Canada	2013
Bruce Squires Award for the Best Research Paper, CMAJ	2011
Scholars Abstract Award, Society for Clinical and Translational Sciences.	2010
Society of General Internal Medicine Clinical Investigator Award (Mid-Atlantic)	2010
Elected, Delta Omega Honorary Public Health Society, Johns Hopkins University	2008
Master Teacher Award, WFUSOM	2008
Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM	2007
Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM	2006
Senior-Resident Scholarship award, Unity Health System, NY	2005
ACP Health and Public Policy Scholarship, NY	2005

Committee Assignments and Administrative Services

American College of Physicians, Massachusetts Chapter, Health Policy Committee	2018
Chairs Advisory Council, Department of Fam Medicine & Comm Hlth	10/2016-present
American College of Chest Physicians, Cough Guideline Expert Panel	2017- present
Associate faculty, Welch Ctr for Prevention, Epi & Clin Research, JHU	2015 to 2016
Associate-Director, Center for Drug Safety and Effectiveness, JHU	2013 to 2016
Affiliate faculty, Center for Hlth Services and Outcomes Research, Johns Hopkins Bloomberg School of Public Health	2012 to 2016
World Health Organization, International Agency of Research on Cancer (IARC) Monograph- 108 Working group, Lyon, France.	2013

Sonal Singh M.D., M.P.H

Preferred Items for Reporting of Systematic Reviews and Meta-analysis of harms Working Group
Alberta Canada. 2012

Member, Health & Human Rights Working Group, JHU Center for Aids Research 2012

Core faculty, Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of
Public Health 2009 to 2016

Core faculty, Evidence-Based Practice Center, JHU 2009 to 2016

Medical Director, Outpatient Clinic, WFUSOM 7/2005-6/2009

Teaching Activities

Classroom

Comparative effectiveness research (2 cr), Johns Hopkins Medicine 2015 to 2016
Role: Developed course in CER for MD and MD/PhD trainees in the CTSA

Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2011 to 2015
Role: Annual lecture in the course for MPH students

Health Economic, Johns Hopkins Bloomberg School of Public Health 2013
Role: Annual lecture in the course for master's students

Pharmacoepidemiology, Johns Hopkins Bloomberg School of Public Health 2011-2015
Role: Annual lecture in the course for Masters and Doctoral students

Evidence-based Medicine, Johns Hopkins University School of Medicine 2012
Role: Course facilitator

Intro to Clinical Investigation, Johns Hopkins University School of Medicine 2012
Role: Annual lecture in the course

Clinical Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2010-2014
Role: Annual lecture in the course

Patient Physician and Society, Johns Hopkins University School of Medicine 2009
Role: Course facilitator

Clinical Teaching

Outpatient medicine 2016-2018

Sonal Singh M.D., M.P.H

Role: Precepting residents and medical students in clinic at University of Massachusetts Medical School

Evidence Based Medicine

2012-2014

Role: Developed a novel course to teach Evidence based Medicine to Osler medical residents at Johns Hopkins University School of Medicine

Outpatient medicine

2005 to 2009

Role: Precepting residents in clinic at Wake Forest University

Inpatient Medicine

2005 to 2009

Role: Precepting internal medicine residents at Wake Forest University

Trainee /Junior Faculty Name	Mentoring Role	Title of Research Project/Paper	Current Position and Institution	Training Period
Univ of Massachusetts				
Mayuko Itofukunaga, MD	Faculty mentor	Systematic review of decision aids for lung cancer screening	Assistant Professor- Pulmonary Medicine and Critical Care	2017-18
Nathaniel, Erskine MD, PhD (student)	Scholarly activity	SR of herpes zoster and cardiovascular disease	MD/PhD Student Umass Med School	2017
Richeek Pradhan MS	Scholarly activity	Comparison of data on Adverse events	Phd Student McGill University	2017-18
Johns Hopkins Univ				
Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student	2018
Geetha Iyer, MD	Faculty mentor	Multiple Pharmacoepidemiologic studies	Doctoral student, HSPH	2015-16
Sathiya Priya Marimathu	Faculty mentor	Generic drugs and patient oriented outcomes	MHS Student, JHMI	2015-16
Yohalakshmi Chelladurai, MD, MPH	RA Scholarly activity	Review of varenicline	Resident physician, Mercer, Atlanta	2013
Hsien-Yen Chang PhD	Faculty mentor	Pharmacoepidemiologic studies	Assistant Scientist at JHU	2011-15
Hasan Shihab, MD, MPH	RA Scholarly activity	Review of GLP-based therapies	Resident, Franklin Square, Baltimore	2013-14
Joshua Sclar, MD, MPH	Scholarly activity	Systematic review of attacks on health workers	General Preventive Medicine Resident	2013
Crystal Ng, MPH	Scholarly activity	Human Rights measures	MPH Student, JHSPH	2013
Ekta Agarwal, MPH	Capstone	Safety of novel anticoagulants	MPH student JHSPH	2013
Meijia Zhou, MHS	Scholarly activity	Adherence to novel anticoagulants	Doctoral student, Univ of Pennsylvania	2013
Kaitlin Hayman, MD	Capstone	SR of the impact of disasters On CVD outcomes	MPH student, JHSPH	2013
Wenze Tang, MPH	Scholarly activity	SCCS analysis of GIB bleeding with dabigatran	Doctoral student, HSPH	2013

Sonal Singh M.D., M.P.H

Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student JHSPH	2018
Shabana Walia MD	Scholarly activity	SR of CVD among refugees and displaced	ER physician, UT Houston	2016-2018
Wake Forest Univ				
Aman Amin, MD	Resident	Inhaled corticosteroids and pneumonia	Practicing internist, NC	2007-09
Apurva Trivedi, MD	Scholarly activity	SSRIs and bleeding	Gastroenterologist	2007-09
Other institutions				
Tonya Breaux-Shropshire PhD, MPH	Scholarly activity	Systematic review	Post-doctoral trainee, UAB	2015
Abhay Kumar, MD	Resident Scholarly activity	Wernicke encephalopathy after gastric bypass: systematic review	Assistant Professor St Louis University	2007

Current Grants and Contracts

Grants

(Ming Tai-Seale)

2/2016-12/2021

PCORI

Improving Patient-Centered Communication in Primary Care: A Cluster Randomized Controlled Trial of the Comparative Effectiveness of Three Interventions

The aim is to compare three interventions to improve patient communication in primary care

Role: co-investigator

(PI Jerry Gurwitz)

08/2018- 09/2019

NIH/NIA-1 R56 AG061813-01

Project Title: Controlling and Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)

Role : co-investigator

The aim is to develop interventions to prevent prescribing cascades among those with Alzheimer's related Dementia (ADRD)

Past Grants

Death Data Exploration

08/01/17- 03/02/18

FDA Foundational Elements 3 HHSF223200910006I

Task Order Number: HHSF22301012T

Efforts to Develop the Sentinel Initiative HHSF223200910006I.

Role (Project Lead)

Effect of Therapeutic Class on Generic Drug Substitutions.

2014-2016

U01FD005267-01 (PI, Jodi Segal)

Sonal Singh M.D., M.P.H

FDA 349,480
Role: Co-Investigator 0.6 CM

Comparative effectiveness Research & The Cochrane Eyes and Vision Group 2013-2016
U01 EY020522 (PI, Kay Dickersin)
NIH/NEI 825,397
Role: Co-Investigator 2.4 CM

Systematic review of gabapentin for neuropathic pain using multiple data sources 2015-2016
(PI, Caleb Alexander)
FDA Center of Excellence in Regulatory Science
Role: Co-Investigator (20% effort)

Integrating multiple data sources for meta-analysis to improve patient-centered outcomes
research 2014-2016
(PI- Dickersin)
PCORI (ME-1303-5785) \$698,174
Role: Advisor (2% effort)

Development of a scale for human rights violations. 2013-2014
(PI, Chaisson & Beyrer)
NIH Johns Hopkins Center for AIDS Research \$ 18,873
Role: Pilot Awardee

Comparative effectiveness review of therapeutic options for obesity in the Medicare population.
Johns Hopkins Evidence Based Practice Center. 2013-2014
PI (Eric Bass)
AHRQ \$125,000
Role: Project Principal Investigator (20% effort)

Center for Excellence in Comparative Effectiveness Education 2012-2013
PHRMA Foundation (PI Jodi Segal) Total Direct Cost: \$250,000
Role: Co-investigator (5% effort)

A multi criteria decision analysis to assist with regulatory decisions around benefit and risk
Partnership in Applied Comparative Effectiveness Science: 2010 to 2013
PI (PI, Jodi Segal).
FDA \$3,509,657
Role: Project Principal Investigator (25% effort)

Combination therapy vs. intensification of statin mono-therapy: An update. 2012-
2013
PI (E. Bass- P.I of EPC.)
AHRQ
Role: Advisor (5% effort)

Troponin cardiac marker during renal impairment. (E. Bass- P.I of EPC.) Agency for Health Care Quality and Research Role: Advisor (5% effort)	2012-2013	
To develop an instrument for attacks on health workers. PI (Len Rubenstein) US Institute of Peace Role: Co-investigator (10% effort)	2012-2013	
To develop an instrument for attacks on health workers. PI (Len Rubenstein) McArthur Foundation Role: Co-investigator (15% effort)	2012-2013	\$434,782
To conduct a benefit and harm assessment of <i>roflumilast</i> in COPD. Johns Hopkins ICTR Role: Co-investigator (5% effort)	2012-2013	
To develop a China-JHU consultation for civil society public health professionals. Open Society Foundation Role: PI (20% effort). Proposal for a public health training program.		2012 \$49,534
PACER. PI (Rothman) Google-Flu Role: Coinvestigator (5%) Systematic reviewer and meta-analysis expert.		2012
Methods for Balancing Benefits and Harms in Systematic Reviews Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Project Task Leader and co-Investigator (10% effort)		2011-2012 \$188,871
Comparative effectiveness review of Meditation Programs for Stress and Wellbeing Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Project Task Leader and co-Investigator (15% effort)		2011-2012 \$375,666
Comparative effectiveness review of prevention of VTE in special populations Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Project Principal Investigator (20% effort)		2011-2012 \$375,666

Sonal Singh M.D., M.P.H

To prevent and respond to gender-based violence (GBV) in refugee and conflict-affected populations. 2010-2011
(PI, Vu & Rubenstein) \$293,946
Role: Co-investigator (10% effort)

Comparative effectiveness review of oral hypoglycemic medications
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2009-2010
AHRQ \$125,000
Role: Co- Investigator (0% effort)

Johns Hopkins Clinical Research Junior Faculty Award. 2009-2012
NIH-KL2
ICTR
Role: Recipient (75% salary support)

Measuring exposure to human rights violations among men who have sex with men.
(PI, Mullany). 2009-2010
Center for Global Health Johns Hopkins \$50,000
Role: Co-investigator (0% effort).

Research ethics for conducting research in vulnerable populations and unstable settings.
(PI, Mills) 2007-2009
CIHR \$99, 887
Role: Co-investigator (10% effort).

Patents None.

Editorial work

Editor-in-chief and founder
BMC Conflict and Health 2007-12

Editorial Board Membership

Evidence Based Medicine (BMJ Group of Journals) 2017-current
Drug Safety 2008-16
American College of Physicians-PIER

Grant review 2012-current

Medical research foundation of New Zealand
Johns Hopkins Center for Public Health and Human Rights
Junior Faculty Research Grants
Medical Research Council of South Africa
Catalina Health Technology Assessment, Spain
Diabetes, UK
Johns Hopkins Medicine Research Council Synergy Awards
Johns Hopkins Institute for Clinical and Translational Research

Peer Review

1. <i>Acta Diabetologica</i>
2. <i>American Heart Journal</i>
3. <i>American Journal of Addictions</i>
4. <i>American Journal of Cardiovascular Drugs</i>
5. <i>American Journal of Managed Care</i>
6. <i>American Journal of Psychiatry</i>
7. <i>Annals of Internal Medicine</i>
8. <i>Annals of Medicine</i>
9. <i>Australian Medical Journal</i>
10. <i>BMJ</i>
11. <i>BMC Clinical Pharmacology</i>
12. <i>British Journal of Clinical Pharmacology</i>
13. <i>Bulletin of the World Health Organization</i>
14. <i>Chest</i>
15. <i>Circulation</i>
16. <i>Canadian Medical Association Journal</i>
17. <i>Clinical Pharmacology and Therapeutics</i>
18. <i>Clinical Trials</i>
19. <i>Cardiovascular Drugs & Therapy</i>
20. <i>Cochrane Collaboration</i>
21. <i>Disasters</i>
22. <i>Diabetologia</i>
23. <i>Drug and Alcohol Dependence</i>
24. <i>Diabetes Obesity and Metabolism</i>
25. <i>Drug Safety</i>
26. <i>Epidemiology</i>
27. <i>European Journal of Neurology</i>
28. <i>European Journal of Pharmacology</i>
29. <i>European Respiratory Journal</i>
30. <i>Expert Opinion in Drug Safety</i>
31. <i>Global Public Health</i>
32. <i>Health Policy</i>
33. <i>International Journal of Epi</i>
34. <i>International Journal of Obesity</i>

35. <i>Journal of the American College of Cardiology</i>
36. <i>Journal of the American Medical Association (5 in last 12 mo)</i>
37. <i>Journal of the American Medical Association-Internal Medicine</i>
38. <i>Journal of Cardiac Failure</i>
39. <i>Journal of Medical Case Reports</i>
40. <i>Journal of the Pancreas</i>
41. <i>Journal of General Internal Medicine</i>
42. <i>Medscape General Medicine</i>
43. <i>Medical Journal of Australia</i>
44. <i>Nephrology Dialysis Transplantation</i>
45. <i>North Carolina Medical Journal</i>
46. <i>Nutrition, Metabolism & Cardiovascular Diseases</i>
47. <i>Pediatric Infectious Disease Journal</i>
48. <i>Pharmacoepidemiology & Drug Safety-Best Reviewer Award 2013</i>
49. <i>Public Library of Science Medicine</i>
50. <i>Primary Care Respiratory Journal</i>
51. <i>Pediatrics</i>
52. <i>Research Synthesis Methods</i>
53. <i>Respiratory Medicine</i>
54. <i>Respirology</i>
55. <i>Southern Medical Journal</i>
56. <i>The Lancet</i>
57. <i>Thorax</i>
58. <i>Tropical Medicine & International Health</i>

Abstracts and Presentations

Oral Presentations

National/International

1. GLP-1-based therapies and risk of pancreatitis: A matched case-control study. 29th International Society of Pharmacoepidemiology, Annual Meeting, Montreal Convention Center, August 26. Montreal, Quebec, Canada.2013
2. GLP-1 based therapies and risk of pancreatitis. 36th SGIM Annual Meeting, Denver, Colorado Posters. 2013
3. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomized controlled trials and observational studies, Society of General Internal Medicine, Minneapolis, Minnesota. 2011

Sonal Singh M.D., M.P.H

4. Odds of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of clinical trials and observational studies, 27th International Society of Pharmacy-Epidemiology, Annual Meeting, Hyatt Regency August 24th. Chicago, Illinois. 2011

Local/Regional

Not applicable

Posters

National/International Meetings

1. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review 2018. International Society of Pharmacoepidemiology, Prague, August 24, 2018.
2. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. Health Care Systems Research Network, San Deigo, March 22, 2017.
3. GLP-1 based therapies and risk of pancreatitis. Pancreatitis, Diabetes, and Pancreatic Cancer Workshop. NIH, Bethesda, Maryland. 2013
4. Thiazolidinediones and risk of bladder cancer: A systematic review and meta-analysis. 36th SGIM Annual Meeting, Denver, Colorado.2013
5. Who is the patient's doctor? Primary care responsibility and co-management relationships among generalist and non-generalist physicians in the National Ambulatory Care Survey, 2002 SGIM 29th Annual Meeting, Los Angeles, California.2006
6. The educational value of case reports from the SGIM national meeting in the internal medicine clerkship. SGIM 29th Annual Meeting, Los Angeles, California.2006
7. Using IPod technology to create a self-guided clinic tour for resident orientation SGIM 29th Annual Meeting, Los Angeles, California.2006
8. Narcotic management in chronic non-malignant pain. A survey of resident's knowledge and attitudes. SGIM 29th Annual Meeting, Los Angeles, California.2006
9. Formulary conversion programs pose a significant risk to patients, SGIM 27th Annual Meeting, Chicago, Illinois.2004

Local regional meetings

Inhaled corticosteroids and the risk of fractures in COPD: A systematic review and meta-analysis. DOM Annual retreat, Johns Hopkins University 2011

Invited presentations

National/International

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. NIH Collaboratory Grand Rounds [Web] March 2, 2018
2. Resurgence of hepatocellular carcinoma in the era of oral direct acting antivirals. Cause or Consequence? Fundamentals of Biomedicine Seminar Series. Texas Tech University Health Sciences Center. El Paso, Texas Dec 13, 2017

Sonal Singh M.D., M.P.H

3. Aligning evidence with preferences: Methodological Challenges and Opportunities. -
Department of Medicine. Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire,
June 15, 2016
 - Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
 - Department of Health Services and Research, Michael De-Bakey VA and Baylor University,
Houston, Texas, May 16, 2016.
 - Meyers Primary Care Institute and Department of Family and Community Medicine,
University of Massachusetts, Massachusetts, March 31 and June 9 2016.
 - VA Center for Chronic Disease and Outcomes Research, Minnesota VA, March 2016.
 - Department of Medicine. University of Central Florida, Orlando, Florida, November 2015.
 - Center for Health Policy and Research Grand Rounds. UC Davis, Sacramento California,
Oct 9 2015;
 - Center for Evidence and Outcomes, Agency for Health Care Research and Quality.
Gaithersville Maryland, August 31, 2015.
4. Risks of Spiriva Respimat outweigh its benefit: A Debate. Inhalation Asia, University of Hong
Kong, Department of Pharmacology and Pharmacy, Hong Kong. 2013
5. GLP-1-based therapies and risk of pancreatitis. Center for Clinical Epidemiology and
Biostatistics Seminar Series, Philadelphia, Pennsylvania. 2013
6. Visiting Professor. Department of Medicine. University of Alabama. 2013
7. Value based health care: Can shared decision making methods get us there? Center for Value
and Effectiveness, Medicine Institute, Cleveland Clinic, Noon Conference.2013
8. Role of Multi-criteria decision analysis in regulatory policy
 - Stanford Prevention Research Center, Stanford University, Palo Alto, Stanford,
California. 2013
 - South Carolina College of Pharmacy, Columbia, South Carolina.2013
 - Department of Medicine. UC Davis, Sacramento, California.2013
 - Department of Clinical Sciences, UT Southwestern, Dallas, Texas.2013
 - Department of Medicine, Geisinger Medical Center, Danville, Pennsylvania. 2013
9. Weighing benefits and risks: Role of shared decision making in type 2 diabetes. CTSA Grand
Rounds, Mayo Clinic, Rochester, Minnesota. 2013
10. Are long-acting muscarinic agents safe for patients with COPD: A Debate. Airway Vista, Asan
Medical Center, Seoul, Korea
11. Academia and industry collaboration for cardiovascular risk mitigation. CBI and Applied
Clinical Trials. 6th Annual Summit, Closing Address. Ritz Carlton, Arlington, Virginia.2012
12. Varenicline: Where are we today? Tobacco Disease Research Program, UCSF. San Francisco
California. Varenicline debate.2012
13. The Maoist Insurgency in Nepal: Health Systems Challenges and Opportunities Conference on
Health in Fragile States: Challenges for the Next Decade. United States Institute of Peace.
Washington DC.2011

Sonal Singh M.D., M.P.H

14. Standards of Care and the Role of Community Advocacy in Clinical Trials. Clinical Research in Developing Countries, IIIrd Annual Marcus Evans Conference, Washington, DC.2008
15. Nepal-A Case study. Integrating public health methods into Conflict Analysis. Norman Patterson School of International Affairs, Carleton University, Ottawa, Canada.2007

Local/Regional

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. Research Seminar Series, Department of Family Medicine and Community Health. University of Massachusetts Medical School. June 15.2018
2. Safety of novel anticoagulants vs warfarin- a case study using complementary study designs. Quantitative Health Sciences, University of Massachusetts Medical School, February 28, 2017
3. GLP-1-based therapies and risk of pancreatic adverse events. University of Maryland, Division of Endocrinology, Metabolism and Nutrition, Grand Rounds, Baltimore, Maryland. 2013
4. Thiazolidinediones and Patient-Oriented Outcomes in Type 2 Diabetes, GIM Grand Rounds. Johns Hopkins University School of Medicine. 2012
5. Patient-Centered Benefit and Risk Assessment. Center for Health Services and Outcomes Research. Johns Hopkins University 2012
6. Varenicline and cardiovascular and neuropsychiatric adverse events: Do benefits outweigh risks? Welch Center Grand Rounds. Johns Hopkins University. 2011
7. The new wave, HIV, Human Rights and Men who have Sex with Men in Nepal. Johns Hopkins Bloomberg School of Public Health, 2011.
8. Network Meta-analysis and Serious Adverse Events. Network Meta-Analysis Methods Workshop. Johns Hopkins Bloomberg School of Public Health. 2010
9. Thiazolidinediones and Cardiovascular Outcomes in Type 2 Diabetes. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2008
10. How Safe Are Our Drugs and How Do We Know? North Carolina ACP, Durham.2008
11. Clinico Pathologic Conference. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
12. Globalization and Health Equity: An emerging Challenge for Academic Medicine. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
13. Thiazolidinediones and Cardiovascular Disease: The Seduction of Common Sense. Epidemiology Seminar Series, Public Health Sciences. Wake Forest University 2007

Workshops and Precourses

1. ISPOR National Meeting, Next Generation Comparative Effectiveness Research- Are we getting organized to facilitate research for the individual patient? Washington, DC May 24, 2016 (workshop)
2. SGIM national meeting, developing high-quality search strategies for systematic reviews. 2010
3. SGIM national meeting, Systematic Review. 2009

Peer reviewed original research publications (reverse chronological order)

Trainees *

1. **Singh S**, Fouyazi H, Anzuoni K, Goldman L, Min JY, Griffin M, Grijalva CG, Morrow JA, Whitmore C, Leonard CE, Selvan M, Nair V, Zhou Y, Toh S, Petrone A, Williams J, Fazio-

- Eynullayeva E, Swain R, Cole DT, Andrade S. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review. *Drug Safety* 2018 (accepted)
2. **Singh S**, Zeiman S, Alan Go, Fortmann S, Wenger N, Fleg JL, Radziszewska B, Stone NJ, Zoungas S, Gurwitz J. Statins for Primary Prevention in Older Adults – Moving toward Evidence-Based Decision-Making. *J Am Geriatr Soc*. 2018 Oct 2. doi: 10.1111/jgs.15449. [Epub ahead of print]
3. Tisminetzky M, Nguyen HL, Gurwitz J, McManus D, Gore J, **Singh S**, Yarzebski J, Goldberg RJ. Magnitude and impact of multiple chronic conditions with advancing age in older adults hospitalized with acute myocardial infarction. *International Journal of Cardiology*. Published Online: August 22, 2018. <https://doi.org/10.1016/j.ijcard.2018.08.062>.
4. Chang HY, **Singh S**, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter-2 (SLGT-2) Inhibitors and Lower Extremity Amputation: A Retrospective Cohort Study. *JAMA Internal Medicine* 2018. 10.1001/jamainternmed.2018.3034 <http://dx.doi.org/10.1001/jamainternmed.2018.3034>. August 13, 2018
5. Birring SS, Kavanagh JE, Irwin RS, Keogh K, Lim KG, Ryu JH; **CHEST Expert Cough Panel**. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. *Chest*. 2018 Jul 20. pii: S0012-3692(18)31075-4. doi: 10.1016/j.chest.2018.06.038. [Epub ahead of print]
6. **Singh S**, Nautiyal A, Loke YK. Oral Direct-acting antivirals and the incidence or recurrence of hepatocellular carcinoma: a systematic review and meta-analysis. *Frontline Gastroenterology* Published Online First: 30 July 2018. doi: 10.1136/flgastro-2018-101017
7. Chang AB, Oppenheimer JJ, Rubin BK, Weinberger M, Irwin RS; **CHEST Expert Cough Panel**. Chronic Cough Related to Acute Viral Bronchiolitis in Children. *Chest*. 2018 Apr 26. pii: S0012-3692(18)30632-9. doi: 10.1016/j.chest.2018.04.019. [Epub ahead of print]
8. Haar RJ, Risko CB, **Singh S**, Rayes D, Albaik A, Alnajjar M, et al. (2018) Determining the scope of attacks on health in four governorates of Syria in 2016: Results of a field surveillance program. *PLoS Med* 15(4): e1002559. <https://doi.org/10.1371/journal.pmed.1002559>
9. Pradhan R, * **Singh S**. Comparison of data on Serious Adverse Events and Mortality in ClinicalTrials.gov corresponding journal articles and medical reviews: A cross-sectional analysis. *Drug Safety* 2018 Apr 11. doi: 10.1007/s40264-018-0666-y. [Epub ahead of print]
10. Wu CH, Tu ST, Chang YF, Chan DC, Chien JT, Lin CH, **Singh S**, Dasari M, Chen JF, Tsai KS. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. *Bone*. 2018 Jun; 111:92-100. doi: 10.1016/j.bone.2018.03.018. Epub 2018 Mar 16
11. Field SK, Escalante P, Fisher DA, Ireland B, Irwin RS; **CHEST Expert Cough Panel**. Cough Due to TB and Other Chronic Infections: CHEST Guideline and Expert Panel Report. *Chest*. 2018 Feb;153(2):467-497. doi: 10.1016/j.chest.2017.11.018. Epub 2017 Nov 28.
12. Erkskine NA, *Tran H, Levin LL, Ulbricht CM, Fingerroth JD, Kiefe CI, Goldberg RJ, **Singh S**. A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. *PLoS One* 2017 Jul 27;12(7): e0181565
13. **Singh S**, Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis of observational studies. *American Journal of Medicine* 2017;130(12):1449-1457

14. Marimuthu S, Iyer G, * Segal JB, **Singh S**. Patient-relevant outcomes associated with generic tamsulosin, levothyroxine, and amphetamine in the FAERS: A pilot study. *J Comp Eff Res*. 2017;6(5):437-447.
15. Iyer G, *Marimuthu S, *Segal JB, **Singh S**. An algorithm to identify generic drugs in the FDA Adverse Event Reporting System. *Drug Safety* 2017 2;40(9):799-808.
16. Tang W, *Chang HY, *Zhou M, * **Singh S**. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. *Sci Rep* 2017 Jan 20; 7:40120. doi: 10.1038/srep40120.
17. Onasanya O, Iyer G, * Lucas E, Lin D, **Singh S**, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 ;4(11):943-956
18. **Singh S**, Wright EE, Kwan AY, Thompson JC, Syed IA, Korol EE, Waser NA, Yu MB, Juneja R. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19(2):228-238
19. Alexander GC, Iyer G, Lucas E, Lin D, **Singh S**. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 ;130(3):293-305
20. Houston KT, Shrestha A, Kafle HM, **Singh S**, Mullany L, Thapa L, Surkan PJ 1. Social isolation and health in widowhood: A qualitative study of Nepali widows' experiences. *Health Care Women Int*. 2016 ;37(12):1277-1288
21. Zorzela, L., Loke, Y.K., Ioannidis, J.P., Golder, S., Santaguida, P., Altman, D.G., Moher, D., Vohra, S., Boon, H., Clark, J., Derry, S., Gallivan, J., Gardiner, P., Gøtzsche, P., Loder, E., Napoli, M., Pilkington, K., Shekelle, P., **Singh S**, Witt, C., Lasserson, T., Wu, T., Shamseer, L., Mulrow, C. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016;352: i157.
22. Fain KM, Yu T, Li T, Boyd CM, **Singh S**, Puhan MA, Evidence Selection for a Prescription Drug's Benefit-Harm Assessment: Challenges and Recommendations, *JCE* 2016 Jun;74:151-7
23. Vu A, Wirtz A, Pham K, **Singh S**, Rubenstein L, Glass N, Perrin N. Psychometric properties and reliability of the Assessment Screen to Identify Survivors Toolkit for Gender Based Violence (ASIST-GBV): results from humanitarian settings in Ethiopia and Colombia. *Confl Health*. 2016 Feb 9; 10:1.
24. Wirtz, AL, Glass N, Pham K, Perrin N, Rubenstein LS, **Singh S**, Vu A. Comprehensive development and testing of the ASIST-GBV, a screening tool for responding to gender-based violence among women in humanitarian settings. *Conflict and Health* 201610:7 DOI: 10.1186/s13031-016-0071-z
25. Hayman KG, *Sharma D, Wardlow RD II, **Singh S**. Burden of cardiovascular morbidity and mortality following humanitarian emergencies: a systematic literature review. *Prehosp Disaster Med*. 2015;30(1):1-9.
26. Chang HY, *Zhou M, * Tang W, * Alexander GC, **Singh S**. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ*. 2015;350:h1585 (editorial by Mary S Vaughn).

27. Abraham NS, **Singh S**, Alexander GC, Heien H, Haas LR, Crown W, Shah ND. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population-based cohort study. *BMJ*. 2015;350:h1857.
28. Chang HY, Hsieh CF, **Singh S**, Tang W, Chiang YT, Huang WF. Anti-diabetic therapies and the risk of acute pancreatitis: a nationwide retrospective cohort study from Taiwan. *Pharmacoepidemiol Drug Saf*. 2015 Jun;24(6):567-75
29. Maruthur NM, Joy SM, Dolan JG, Shihab HM, **Singh S**. Use of the Analytic Hierarchy Process for medication decision-making in type 2 diabetes. *PloS One*. 2015 ;10(5): e0126625.
30. Breaux-Shropshire TL, * Judd E, Vucovich L, Shropshire TS, **Singh S**. Does home blood pressure monitoring improve patient outcomes? A systematic review comparing home and ambulatory blood pressure monitoring on blood pressure control and patient outcomes. *Integrated Blood Pressure Control* 2015 3; 8:43-9.
31. Zhou M, *Chang HY, Segal JB, Alexander GC, **Singh S**. Adherence to a novel oral anticoagulant among patients with atrial fibrillation. *J Manag Care Spec Pharm*. 2015; 21(11):1054-62.
32. Puhan MA, Yu T, Stegeman I, Varadhan R, **Singh S**, Boyd CM. Benefit-Harm Analysis and Charts for Individualized and Preference-Sensitive Prevention - The example of low dose aspirin for primary prevention of cardiovascular disease and cancer. *BMC Med*. 2015; 13:250.
33. Mayo-Wilson E, Hutfless S, Li T, Gresham G, Fusco N, Ehmsen J, Heyward J, Vedula S, Lock D, Haythornthwaite J, Payne JL, Cowley T, Tolbert E, Rosman L, Twose C, Stuart EA, Hong H, Doshi P, Suarez-Cuervo C, **Singh S**, Dickersin K. Integrating multiple data sources (MUDS) for meta-analysis to improve patient-centered outcomes research: a protocol for a systematic review. *Syst Rev* 2015; 4(1).
34. Morton MJ, DeAugustinis ML, Velasquez CA, **Singh S**, Kelen GD. Developments in Surge Research Priorities: A Systematic Review of the Literature Following the Academic Emergency Medicine Consensus Conference, 2007-2015. *Acad Emerg Med*. 2015 ;22(11):1235-52.
35. *Shihab HM, Akande T, Armstrong K, **Singh S**, Loke YK. Risk of pancreatic adverse events associated with the use of glucagon-like peptide-1 receptor agonist and dipeptidyl peptidase-4 inhibitor drugs: A systematic review and meta-analysis of randomized trials. *World J Meta-Anal* 2015; 3(6): 254-283
36. Haut ER, Garcia LJ, Shihab HM, Brotman DJ, Stevens KA, Sharma R, Chelladurai Y, Akande TO, Shermock KM, Kebede S, Segal JB, **Singh S**. The Effectiveness of Prophylactic Inferior Vena Cava Filters in Trauma Patients: A Systematic Review and Meta-analysis. *JAMA Surg* 2014; 149(2):194-202
37. **Singh S**, Ambrosio M, Semini I, Tawil O, Saleem M, Imran M, Beyrer C. Revitalizing the HIV response in Pakistan: a systematic review and policy implications. *Int J Drug Policy* 2014;25(1):26-33.
38. Turner LW, Nartey D, Stafford RS, **Singh S**, Alexander GC. Ambulatory Treatment of Type 2 Diabetes Mellitus in the United States, 1997-2012. *Diabetes Care*. 2014;37(4):985-92
39. Yu T, Fain K, Boyd C, Varadhan R, Weiss CO, Li T, **Singh S**, Puhan MA. Benefits and harms of roflumilast in moderate to severe COPD. *Thorax* 2014; 69:616-22

40. Turner RM, Kwok CS, Chen-Turner C, Maduakor CA, **Singh S**, Loke YK. Thiazolidinediones and associated risk of Bladder Cancer: a Systematic Review and Meta-analysis. *Br J Clin Pharmacol.* 2014 78(2):258-7
41. Goyal M, **Singh S**, Sibinga E, Gould NF, Rowland-Seymour A, Sharma R, Berger Z, Sleicher D, Maron D, Shihab HM, Ranasinghe PD, Linn S, Bass EB, Haythornthwaite JA. Meditation Programs for Psychological Stress and Well-being: A Systematic Review and Meta-analysis. *JAMA Intern Med.* 2014 174(3):357-68 (editorial by Gorroll. Moving towards Evidence Based Complementary Care)
42. Vu A, Adam A, Wirtz A, Pham K, Rubenstein L, Glass N, Beyrer C, **Singh S**. The Prevalence of Sexual Violence among Female Refugees in Complex Humanitarian Emergencies: a Systematic Review and Meta-analysis. *PLOS Currents Disasters.* 2014 Mar 18. Edition 1.
43. Wirtz AL, Pham K, Glass N, Loochkarth S, Kidane T, Cuspoca D, Rubenstein LS, **Singh S**, Vu A. Gender-based violence in conflict and displacement: qualitative findings from displaced women in Colombia. *Confl Health.* 2014; 8:10.
44. *Haar RJ, Footer KH, **Singh S**, Sherman SG, Branchini C, Sclar J, Clouse E, Rubenstein LS. Measurement of attacks and interferences with health care in conflict: validation of an incident-reporting tool for attacks on and interferences with health care in eastern Burma. *Conflict and Health.* 2014, 8:23.
45. Cavallazzi R, El-Kersh K, Abu-Atherah E, **Singh S**, Loke YK, Wiemken T, Ramirez J. Midregional proadrenomedullin for prognosis in community-acquired pneumonia: A systematic review. *Respir Med.* 2014 ;108(11):1569-1580.
46. Dorsey ER, Brocht AFD, Nichols PE, Darwin KC, Anderson KE, Beck CA, **Singh S**, Biglan KM, Shoulson I. Depressed mood and suicidality in individuals exposed to tetrabenazine in a large Huntington disease observational study. *Journal of Huntington's Disease* 2013; 2(4): 509-515.
47. Ter Riet G, Chesley P, Gross AG, Siebeling L, Muggensturm P, Heller N, Umbehr M, Vollenweider D, Yu T, Akl EA, Brewster L, Dekkers OM, Mühlhauser I, Richter B, **Singh S**, Goodman S, Puhan MA. All That Glitters Isn't Gold: A Survey on Acknowledgment of Limitations in Biomedical Studies. *PLoS One* 2013 ;8(11): e73623.
48. Wirtz AL, Glass N, Pham K, Rubenstein LS, **Singh S**, Vu A. Development of a screening tool to identify female survivors of gender-based violence in humanitarian settings: qualitative evidence from research among refugees in Ethiopia. *Conflict and Health* 2013, 7:13.
49. Loke YK, Ho R, Smith M, Wong O, Sandhu M, Sage W, **Singh S**. Systematic review evaluating cardiovascular events of the 5-alpha reductase inhibitor - Dutasteride. *J Clin Pharm Ther* 2013 38(5):405-15
50. Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. Collaborators: Stewart BW, Biggar RJ, Lachenmeier DW, **Singh S**, Tsuda H, Baguley B, Marques MM, Tseng CH, Knight TL, Beland FA, Betz JM, Carcache de Blanco EJ, Cunningham ML, Dunnick JK, Guo L, Jameson CW, Karagas M, Lunn RM, McCormick DL, Witt KL, Zhou S. Carcinogenicity of some drugs and herbal products. *Lancet Oncol.* 2013; 14(9):807-8.

51. Maruthur NM, **Joy S**, Dolan J, Segal JB, Shihab HM, Singh S. Systematic assessment of benefits and risks: study protocol for a multicriteria decision analysis using the Analytic Hierarchy Process for comparative effectiveness research. *F1000 Research*. 2013 Jul 24; 2:160
52. Loke YK, **Singh S**. Risk of acute urinary retention associated with inhaled anticholinergics in patients with chronic obstructive lung disease: systematic review. *Therapeutic Advances in Drug Safety* 2013, 4: 19-26.
53. **Singh S**, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus: A Population-Based Matched Case-Control Study. *JAMA Intern Med* 2013 28; 173:1843-4. (editorial by Peter Butler in JAMA Internal Medicine and Edwin Gale in the BMJ)
54. **Singh S**, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Thiazolidinedione use and risk of hospitalization for pneumonia in Type 2 Diabetes Mellitus: A Population-Based Matched Case-Control Study. *F1000Research* 2013 2:145.
55. Brotman DJ, Shihab HM, Prakasa KR, Kebede S, Haut ER, Sharma R, Shermock K, Chelladurai C, **Singh S**, Segal JB. Pharmacological and Mechanical Strategies for Preventing Venous Thromboembolism after Bariatric Surgery: A Systematic Review and Meta-analysis. *JAMA Surg* 2013 148(7):675-86.
56. Kebede S, Prakasa KR, Shermock K, Shihab HM, Brotman DJ, Sharma R, Chelladurai Y, Haut ER, **Singh S**, Segal JB. A systematic review of venous thromboembolism in patients with renal insufficiency, obesity, or on antiplatelet agents. *J Hosp Med* 2013 ;8(7):394-401.
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58. **Singh S**, Loke YK, Enright P, Furberg CD. The pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergics. *Thorax* 2013 68: 114-116.
59. Denizard-Thompson NR, **Singh S**, Stevens SR, Miller DP, Wofford JL. IPod™ technology for teaching patients about anticoagulation: a pilot study of mobile computer-assisted patient education. *Prim Health Care Res Dev* 2012 13: 42-7.
60. Treadwell JR, **Singh S**, Talati R, McPheeters ML, Reston JT. A Framework for “Best Evidence” Approaches in Systematic Reviews. *J Clin Epidemiol* 2012; 65: 1159-62.
61. Moore T, Glenmullen J, Maltzberger JT, Furberg CD, **Singh S**. Suicidal Behavior and Depression in Smoking Cessation Treatments. *PLOS One* 2011; 6: e27016.
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None

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Correspondence

1. **Singh S**, Suchard MA. Pioglitazone Use and Risk of Bladder Cancer. *JAMA*. 2015 Dec 15; 314(23):2567-8.
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Development of major curricular offerings.

Sonal Singh M.D., M.P.H

2 credit Course for MD and MPH in comparative effectiveness research for the Johns Hopkins
ICTR 2015-2016

Sonal Singh M.D., M.P.H

Sonal Singh MD, MPH received his MD from Patna Medical College India (1999). He completed internal medicine residency training at Unity Health System, affiliate of Strong Memorial Hospital Rochester, NY. (American Board of Internal Medicine 2005) He obtained an MPH from Johns Hopkins Bloomberg School of Public Health (2008) and completed subsequent research training at the Johns Hopkins Hospital (2012) as a Junior Faculty Research Scholar supported by the National Institute of Health. He was the Associate Director for the Center for Drug Safety and core faculty Evidence Based Practice Center and the Center for Public Health and Human Rights at Johns Hopkins University. He has taught and held faculty appointments at Wake Forest University School of Medicine and Johns Hopkins University. He has received numerous awards including the Senior Scholarship Award from the Unity Health System (2005), Tinsley R Harrison Teaching Award for Education at Wake Forest University in 2007, Master Teacher Award at Wake Forest University (2008), Mid-Atlantic Society of General Internal Medicine Clinician Investigator of the Year Award (2010), the Bruce P Squires Award for the best research paper of the year from the Canadian Medical Association Journal (2011) and the third best student abstract award from the International Society of Pharmacoepidemiology (2013). He conducts clinical research with a focus on evidence synthesis, drug safety and shared decision making. Dr Singh has conducted research in several countries and has published more than 150 academic manuscripts to advance research and clinical care. His research efforts have been supported by the NIH, FDA, Agency for Health Care Research and Quality and the Patient Centered Outcome Institute and various private foundations. His research has been published in *Science*, *NEJM*, *Journal of the American Medical Association*, *Annals of Internal Medicine*, *Lancet* and *the British Medical Journal*, and featured in various outlets including *Nature Medicine*, *NYTIMES*, *CNN*, *Washington Post* and *the Wall Street Journal*. He currently serves on the editorial board of the *Evidence Based Medicine Journal* published by the BMJ, as a panel member of the American College of Chest Physician guideline writing group, and American College of Physicians Health Policy committee (Massachusetts chapter) He has served as a consultant to the World Bank, World Health Organization International Agency for Research Cancer, the Agency for Health Care Research and Quality, pharmaceutical sponsors and research firms and several non-governmental organizations. He is a practicing general internist with a passion for managing patients with complex medical conditions.

EXHIBIT B

Trial Testimony

I have not provided trial testimony.

Expert deposition (last 5 years)

1. US District Court of South Carolina, Charleston; *In Re Lipitor (Atorvastatin Calcium) marketing, sales practices and products liability litigation*, MDL No. 2:14-mn-02502-rmg, April 28, 2015; supplementary deposition, in 2016.
2. US States District Court, Eastern District Court of California; *Kristi Lauris Individually and as Successor in Interest to the Estate of Dainis Lauris; vs Defendants Novartis AG*, Case No. 1:16 cv 00393 –LJO-SAB. Case 2:17-cv-14302-RLR Document 49 Entered on FLSD Docket, 2017.
3. Circuit Court of Camden County, Missouri; *Grace Arlene Rahmoeller v. Walmart Stores, Inc. and Nicholas B. Collins*, Case No.: 15CM-CC00238, April 16, 2018.
4. US District Court, Southern District of Florida, *Dennis McWilliams and Lori McWilliams v. Novartis AG and Novartis Pharmaceuticals Corp.*, Case No. 17-14302, May 2, 2018.
5. *Mary Brufett and Jefferey Brufett, vs Iskra Pusic, MD, Keith E. Stocker Goldstein and Washington University*, Cause No 1622-CC01117 (Division 8), May 10, 2018.
6. US District Court Northern District of California, San Francisco Division; *In Re: Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation*, Civil Case No.: 3:16-md-02691-RS, MDL No. 2691, August 9, 2018.

Exhibit 11

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**


**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
ELLEN BLAIR SMITH, MD**

Date: November 16, 2018



Ellen Blair Smith, MD

As a physician who specializes in the treatment of women with cancer (including ovarian cancer), I was asked to provide professional opinions on the question of whether the genital use of talcum powder products can cause ovarian cancer. I was also asked, if I found this to be the case, to further provide opinions on the biological mechanism(s) for this effect.

BACKGROUND AND QUALIFICATIONS

My name is Ellen Blair Smith. My attached CV reports my education and medical training. I practiced gynecologic oncology in Charlottesville, Virginia from July 1984 until February 1987 as an assistant professor at the University of Virginia. I then left academic medicine to open my own private practice of gynecologic oncology in Austin, Texas. That practice involved care of women known or suspected to have gynecologic cancers and continued for more than 28 years. During these years, I was responsible for all aspects of the care of hundreds of women with epithelial ovarian cancer. That care involved diagnosis, preoperative, surgical, and postoperative care, chemotherapy selection and administration and post-treatment care and surveillance. All too often post-treatment surveillance led to the diagnosis of recurrent cancer and the treatment cycle resumed. All too often, after months or years (up to 21 years of care for one patient), I provided end-of-life care for my patients.

My dissatisfaction with the inadequacies of screening systems to detect ovarian cancer early led me to follow enthusiastically the discoveries of genes that increase the risk of ovarian cancer and to aggressively promote the detection of such genes. Before these tests were commercially available, I worked with geneticist-physicians at the University of Pennsylvania and Duke University to detect these genes in my patients with ovarian cancer and their daughters. I was an early advocate of risk-reducing salpingo-oophorectomy and lectured throughout Texas by invitation of the Texas Medical Association. In 2004, Myriad Genetics (which had patented the BRCA test) asked me to be its first gynecologic oncologist speaker. Until roughly 2011, I delivered many lectures to gynecologic colleagues throughout the US.

In November 2001, I took a leave of absence and moved to Paris, France, with my children while my husband pursued a Guggenheim fellowship there. While there, I returned to the US to attend the Society of Gynecologic Oncologists to hear the latest research in ovarian cancer presented. I also attended a European Cancer conference in Paris and was excited to first hear the results of the Scottish Randomised Trial in Ovarian Cancer (SCOTROC), a large international randomized trial comparing two different chemotherapy regimens for the treatment of epithelial ovarian cancer ovarian cancer trial in which I enrolled patients. I returned to my practice in August of 2002.

To enhance the end of life care of my gynecologic oncology patients, I pursued further education in Hospice and Palliative Care, passing the written examination to become board certified in 2010. I retired from my gynecologic oncology practice in December of 2015. In April of 2017, I returned to patient care as medical director of Halcyon Home Hospice. In my role with a hospice organization, I continue to care for patients with ovarian and other cancers. My CV is attached as Exhibit A.

METHODOLOGY

In preparing this report, I began with a comprehensive review of the medical literature. I relied on PubMed searches on many topics, including talc and ovarian cancer, as well as searched authors. I then read many of the references of the articles cited in those papers. I sometimes followed this research with searches on Google or Google Scholar on the same subjects to assure that I had found all relevant references. This literature included epidemiological studies, review articles, mechanistic articles and opinion articles on this topic and related subjects. I additionally reviewed information, including Johnson & Johnson and Imerys company documents that I either requested or considered relevant to my opinions. These were provided by plaintiffs' attorneys. Finally, I drew on my own educational resources, as well as my education, training, and experience caring for patients with ovarian cancer. This is the same methodology and scientific rigor that I have used regularly in my professional career and clinical practice, to explore and understand a topic of interest.

OVERVIEW OF OVARIAN CANCER

Cancers of the ovary may arise from the epithelium/mesothelium covering the ovary, called epithelial ovarian cancer (EOC); from the oocytes of the ovary, called germ cell tumors; or, more rarely, from the hormone-producing cells of the ovary, the sex cord-stromal tumors. This report addresses EOC, the type of ovarian cancer associated with talcum powder exposure.

Pathogenesis

The history as to the origin of ovarian cancer must be divided into before 2008 and after 2008. Before 2008, incessant ovulation and the repair of the monthly breaks in ovarian surface epithelium was believed to be responsible for EOC. (Fathalla 1971). That more DNA errors would be generated with more ovulation defects made intuitive sense and seemed to be supported by the epidemiologic evidence of higher parity (ovulation free windows) decreasing risk of EOC (La Vecchia 2017). Furthermore, the first generation of high estrogen oral contraceptives that blocked ovulation also decreased ovarian cancer. (Havrilesky et al. 2013) Levanon proposed that EOC is, in fact, two different diseases with two etiologies; the premalignant state of Type II was, as yet, unidentified. Budding molecular data support this division. (Levanon, Crum, and Drapkin 2008).

Until 2008, EOC was thought distinct from fallopian tube cancer and primary peritoneal cancer. While the cell of origin for all these cancers appears similar, many papers were published and conventions defined to separate them. The pioneering work of scientists/physicians at Brigham and Women's and the Dana Farber revealed that many EOCs arise in the fallopian tube and metastasize to the ovary and/or peritoneum, at least in women who harbor genetic homologous repair defects. (Levanon, Crum, and Drapkin 2008). Both Fathalla and the researchers at Brigham and Women's have updated and more clearly defined their hypotheses in light of the increased role of fallopian tube epithelium in EOC and growing molecular data. (Levanon, Crum, and Drapkin 2008; Fathalla 2013). Dubeau and Drapkin include and support the role of extrauterine Mullerian epithelium, as well as tubal and ovarian epithelium, in their hypotheses of pathogenesis of EOC. (Dubeau and Drapkin 2013). For our purposes, we consider epithelial

cancers of the ovary, fallopian tubes, and peritoneum to be a single entity. All are associated with talcum powder usage

The quest for a molecular understanding of the ways EOC arise is ongoing, but has also been described extensively. There are certain factors that can initiate the cascade of DNA changes that cause unregulated proliferation, acquisition of more DNA damage, and inhibition of programmed cell death (apoptosis) - the normal fate of abnormal cells in a healthy system. For example, loss of TP53 (a gene essential for regulating cell division and preventing tumor formation), function has been shown to appear early in the genesis of serous EOC. (Chien et al. 2015).

Risk Factors

Generally accepted risk factors for EOC, in addition to talcum powder and asbestos, include inherited gene mutations, family history, obesity, nulliparity, advanced age, history of endometriosis, infertility, polycystic ovarian syndrome, intrauterine devices, pelvic inflammatory disease, early menarche and late menopause. Additionally, there are factors that are recognized as protective. These include tubal ligation/sterilization (TS), oral contraceptive use, salpingectomy, salpingo-oophorectomy, hysterectomy, and breast feeding. (Hunn and Rodriguez 2012; Mallen, Townsend, and Tworoger 2018; Park et al. 2018; Folkins et al. 2018). Risk factors are not mutually exclusive. They can be cumulative, additive, and synergistic. (Vitonis, Titus-Ernstoff, and Cramer 2011; S. Wu et al. 2018).

Inherited gene mutations, such as BRCA-Fanconi anemia pathway and Lynch syndrome mismatch repair genes, are discussed in another section.

The Ovarian Cohort Consortium pooled data from 21 prospective cohort studies on 1.3 million women. (Wentzensen et al. 2016). In these studies, 5584 women were diagnosed with EOC and risk comparisons were made for parity, oral contraception use, breast feeding, age at menarche, age at menopause, menopausal HRT use, tubal ligation, endometriosis, first degree family history of breast cancer, first degree history of ovarian cancer, BMI, height, and smoking). In a group this large, histologic subclassification could be done and associations were made for serous/poorly differentiated EOC, endometrioid EOC, clear cell EOC and mucinous EOC. One thousand EOC patients had “other” or missing histologic information. Multiparity decreased risk in all ovarian cancer subtypes. Oral contraceptive use for 5 years and for 10 years decreased risk in all but mucinous tumors. Late menopause increased risk in only endometrioid and clear cell cancers.

Diagnosis

The diagnosis of EOC may occur at surgery for a pelvic mass, incidentally at surgery for another reason, or by cytologic evaluation of paracentesis of ascites.

Staging

Ovarian cancer, regardless of cell type, is staged surgically. By convention, we use International Federation of Gynecology and Obstetrics (FIGO) staging. The staging system changes every 10-

15 years as data allowing discrimination are reviewed. It was always my practice to note in a patient's chart the original stage and year of that staging versus contemporary stage.

STAGE I: Tumor confined to ovaries				
OLD			NEW	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites.		IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries otherwise like IA.		IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites.		IC Tumor limited to 1 or both ovaries	
			IC1	Surgical spill
			IC2	Capsule rupture before surgery or tumor on ovarian surface.
			IC3	Malignant cells in the ascites or peritoneal washings.

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer					
OLD			NEW		
IIA	Extension and/or implant on uterus and/or Fallopian tubes		IIA	Extension and/or implant on uterus and/or Fallopian tubes	
IIB	Extension to other pelvic intraperitoneal tissues		IIB	Extension to other pelvic intraperitoneal tissues	
IIC	IIA or IIB with positive washings/ascites.				

****Old stage IIC has been eliminated****

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes				
OLD			NEW	
IIIA	Microscopic metastasis beyond the pelvis.		<i>IIIA (Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)</i>	
			IIIA1	<i>Positive retroperitoneal lymph nodes only</i>
			IIIA1(i)	<i>Metastasis ≤ 10 mm</i>
			IIIA1(ii)	<i>Metastasis > 10 mm</i>
			IIIA2	<i>Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes</i>
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm in greatest dimension.		IIIB	<i>Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.</i>
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension and/or regional lymph node metastasis.		IIIC	<i>Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.</i>

STAGE IV: Distant metastasis excluding peritoneal metastasis				
OLD			NEW	
IV	Distant metastasis excluding peritoneal metastasis. Includes hepatic parenchymal metastasis.		IVA	<i>Pleural effusion with positive cytology</i>
			IVB	<i>Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)</i>

FIGO Ovarian Cancer Staging Effective Jan. 1, 2014.¹

Treatment

The treatment of ovarian cancer is usually straight-forward: surgically remove all the visible cancer, establish locations of invisible cancer (microscopic metastases, define best treatment and prognosis, then treat -in the majority of cases - with a taxane and a platinum chemotherapy doublet. (Vasey et al. 2004; Armstrong et al. 2006).

However, seventy-five percent of ovarian cancer cases present with metastases to the upper abdomen or beyond. Suboptimal debulking (leaving grossly visible tumor) has no survival benefit over primary chemotherapy. (Horowitz et al. 2015). The physicians at MD Anderson established a protocol for preoperative laparoscopy and the opinions of two trained gynecologic oncologists, in concert with clinical and laboratory findings, to judge whether a tumor was resectable. (Nick et al. 2015). These “debulking” surgeries are quite complex, require specialized training, and often necessitate consultation from other surgical specialties.

¹ https://www.sgo.org/wp-content/uploads/2012/09/FIGO-Ovarian-Cancer-Staging_1.10.14.pdf

Chemotherapy with a platinum and a taxane follows. These drugs may be delivered intravenously or intraperitoneally. Usually, six cycles of chemotherapy are given. Remission occurs in over 70% of patients, as evidenced by CT scans, physical examination, and CA125 (a clinically used biomarker for screening and detection) levels. Surveillance begins.

In patients with Stage III and IV (typically 75% of patients with EOC), recurrence will follow in 5-24 months. Then we evaluate again for surgery (isolated focal recurrence versus multifocal or unresectable recurrence) and additional chemotherapy. (Rasool et al. 2010; Parmar et al. 2003).

This cycle typically continues until my patient's tumor has become resistant to platinum and two other agents. At that time, the probability of her tumor responding to any standard chemotherapy is essentially nonexistent. We discuss clinical trials and/or end-of-life care. Regardless of her treatment choices, she dies in 6-12 months. Her death is protracted, usually from starvation, due to multiple bowel obstructions. Ideally, pain is controlled.

5 Year Survival Rates

The following are 5-year survival rates according to the American Cancer Society Website. As the new FIGO staging just started in 2014, 5-year data is not yet available.

I 78%

IA 93%

IB 91%

IC 84%

II 61%

IIA 82%

IIB 72%

IIC 67%

III 28%

IIIA 63%

IIIB 53%

IIIC 41%

IV 19%.²

Modern surgery and chemotherapy have changed the natural history of ovarian cancer. Late recurrence (after 5-year) is common. Ten-year survival does not mean cure. I have personally treated late recurrences after ten years of remission. Others have reported these findings as well. (Baldwin et al. 2012; Tewari et al. 2015)

² <https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html>

OVARIAN CANCER GENETICS

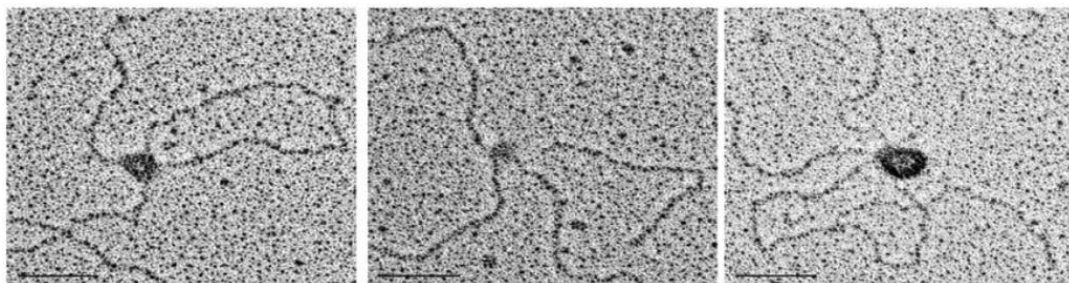
All cancer is genetic; that is, cancer involves DNA changes occurring in the chromosomes of a cell that was initially normal. For epithelial cancers, this is usually a series of mutations, DNA breaks, alterations (such as methylation), deletions, rearrangements or DNA amplification. These changes do not necessarily progress linearly. Watson reviewed some of these complexities in a recent article in *Nature*. (Watson et al. 2013).

A Cancer Genome Atlas Research Network (TCGA) study published in 2011 analyzed 489 high grade serous ovarian cancers (HGSOC). Exon sequencing of 316 of these tumors was performed. It identified the nearly universal (96%) presence of somatic mutations in the gene TP53 in HGSOC. That mutation seems to be a first step towards the development of EOC. Ovarian cancers occur in <3% of women with germline, heritable TP53 mutations; breast cancer is much more frequently occurring. (K. D. Gonzalez et al. 2009). Genes in homologous repair pathway were mutated in 49% (with better prognosis for those with germline mutations as opposed to somatic mutation or methylation). The FOXM1 transcription factor network was activated in 87%. This family of genes is involved in regulating cell cycle and differential gene expression. (Hannenhalli and Kaestner 2009; X. Chen et al. 2013).

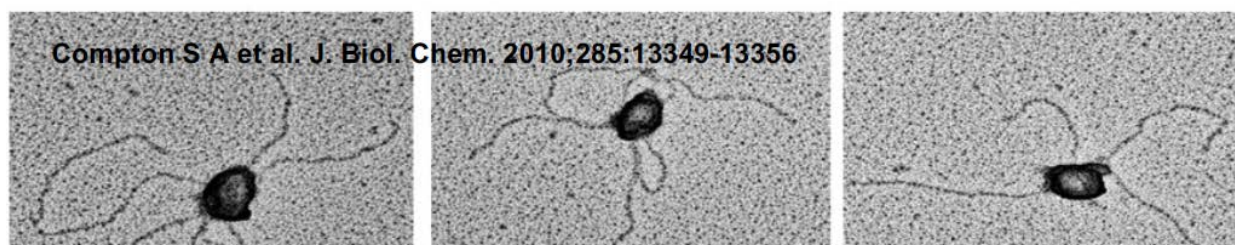
Interest in the homologous repair pathway has exploded since Mary Claire King's identification of what we now know to be the tumor suppressor gene, BRCA1. (Hall et al. 1990).

Homologous DNA repair is double stranded DNA repair breaks. This pathway includes multiple genes including BRCA1, BRCA2, Rad 51B, Rad 51C, Rad 51D, BRIP1, PALB2 and others. The protein products of this family of multiple genes work together to repair DNA. (Compton, Ozgür, and Griffith 2010; Thai et al. 1998). Binding of BCDX2 or CX3 to Holliday Junction DNA CX3 (A) or BCDX2 (B) was incubated with Holliday junction templates, mounted onto carbon-coated copper grids, and rotary shadowcast with tungsten for visualization by EM. Images are shown in reverse contrast. (Compton, Ozgür, and Griffith 2010).

A



B



The ring structure in A is a complex of Rad 51C and Xrcc3. The ring structure in B is a complex of Rad 51B, Rad 51C, Rad 51D and Xrcc2.

Germline deficiencies in any of these genes have been shown to result in an increased risk of EOC. Why? Knudson answered that in simple terms (Knudson 1971). To be born deficient in one half of a DNA repair enzyme is to be born one step closer to cancer; target cancers appear earlier and more frequently. Many early studies note the increased incidence of breast cancer with BRCA1 and BRCA2 germline mutations carriers: over 80% by age 70. (Ford et al. 1998). They also give the increased risks of ovarian cancer: for BRCA1, 39% by age 70, and for BRCA2, 11% by age 70 studied 1915 patients with ovarian cancer and detected germline mutations in BRCA1 and BRCA2, RAD51B, Rad51D, PALB2, BARD1, BRIP1 (the HR repair pathway), as well as the genes involved in Lynch Syndrome. (Antoniou et al. 2003; Norquist et al. 2016).

Penetrance is the phenotypic expression of underlying genetic aberrations. Why does one woman with a BRCA1 mutation exhibit breast and/or ovarian cancer while another woman with the SAME mutation does not? Penetrance is influenced by environmental and genetic factors. For example, epidemiologic studies have shown that breast feeding and tamoxifen use decrease the risk of manifesting breast cancer in carriers of BRCA1 mutations. (Friebel, Domchek, and Rebbeck 2014). This same review and meta-analysis shows that oral contraceptives use decreases risk for ovarian cancer in BRCA1 and BRCA2 mutation carriers. Other known risk factors can interact with individuals who have an inherited gene mutation to increase the risk. In other words, women with BRCA and other hereditary gene mutations, are at least as susceptible to other reproductive, environmental, or inflammatory risk factors as women who do not have mutations. This would be expected with BRCA mutation carriers exposed to talcum powder products.

Factors that decrease penetrance may be external or environmental factors, as mentioned above, or may be intrinsic factors, genetic, or epigenetic. Rebbeck et al. demonstrated that the location of the mutation in these huge BRCA genes is a determinant of risk of manifestation of breast and/or ovarian cancer. (Rebbeck et al. 2015). Genetic and epigenetic modifiers became the focus of the CIMBA (Consortium of Investigators of Modifiers of BRCA1/2). (CIMBA et al. 2007). This international consortium of sixty groups of researchers are identifying genetic modifiers to BRCA breast and ovarian cancer risks as single nucleotide polymorphisms (SNPs) in nonBRCA genes. (Ding et al. 2012; Ramus et al. 2012). Such SNPs modify penetrance. Epigenetic changes such as methylation in promoter regions of genes also affect risk of ovarian cancer development.

EPIDEMIOLOGICAL STUDIES

The first epidemiological study was published in 1982 by Cramer, et al, Cancer (1982) 50:372 “Ovarian Cancer and Talc: A Case-Control Study.” (D. W. Cramer et al. 1982). Since that time, there have been numerous additional epidemiological studies.

The Meta-analyses and Pooled Study

Harlow et al, 1992:

This study (of which Cramer is a coauthor) offers the first meta-analysis of the perineal talcum powder use and risk of ovarian cancer in their case-control study of 235 Boston-area women hospitalized in ten area hospitals. Controls were selected from the population and generated from “townbooks” by random number generation selecting the book page and age matched. “Ever” perineal talcum powder use vs none generated a OR of 1.5 (95% CI 1.0-2.1). The meta-analysis follows:

Table 6. Odds Ratios With 95% Confidence Intervals of Ovarian Cancer in Relation to Any Perineal Exposure to Talc as Reported in Previous Epidemiologic Studies

Author(s) (year)	Cases		Controls		Crude OR	95% CI
	Total	Talc exposure	Total	Talc exposure		
Cramer et al ⁴ (1982)	215	92 (42.8%)	215	61 (28.4%)	1.9	1.3–2.9
Hartge et al (1983)*	135	67 (49.6%)	171	100 (58.5%)	0.7	0.4–1.1
Whittemore et al ⁵ (1988)	188	98 (52.1%)	539	248 (46.0%)	1.4	0.9–2.0
Harlow and Weiss ⁶ (1989) [†]	116	49 (42.2%)	158	64 (40.5%)	1.1	0.7–2.1
Booth et al ⁷ (1989)	217	141 (65.0%)	434	256 (59.0%)	1.3	0.9–1.9
Harlow et al (1992) (current study)	235	114 (48.5%)	239	94 (39.3%)	1.5	0.9–1.8
All studies [‡]	1106	561 (50.7%)	1756	823 (46.9%)	1.3	1.1–1.6

The authors conclude that “there is an association, albeit modest, between ovarian cancer and peritoneal talc use” They state that this association may be due to asbestos contamination in talcum powder produced before 1976. This study was supported by an NCI grant. (Harlow et al. 1992).

Gross and Berg, 1995

These investigators analyzed 9 case-control studies (D. W. Cramer et al. 1982; Hartge et al. 1983; Whittemore et al. 1988; Booth, Beral, and Smith 1989; Harlow and Weiss 1989; Y. Chen et al. 1992; Harlow et al. 1992; Rosenblatt, Szklo, and Rosenshein 1992; Tzonou et al. 1993) and combined those studies with preliminary (and mathematically manipulated) data from Hankinson et al’s 1993 report on the Nurses’ Health Study. The Nurses’ Health Study was not completed until 1996; talc use was not queried in the first 8 years of the study. By Gross’ and Berg’s estimate the RR of “ever genital talc use” vs “never” use is 0.6 (95% CI 0.38-1.02). In fact, that is a low RR as the Nurses’ study showed and overall RR of ever vs never use and epithelial ovarian cancer of 1.09 (95% CI 0.86-1.37). (Gertig et al. 2000, see below).

192 *Gross and Berg***TABLE 3. Results of the Meta-Analyses**

Analysis	Studies used	<i>Q</i> (degrees of freedom)	RR (95% CI)
Crude risk, both tumor types	All	11.884 (8)	1.27 (1.09–1.48)
Adjusted risk, both tumor types	CRAM, HART, WHIT, HAR1, HAR2, CHEN, and TZON	9.043 (6)	1.31 (1.08–1.58)
Crude risk, epithelial tumors	HART, WHIT, BOOT, HAR2, ROSE, CHEN, and TZON	7.19 (6)	1.20 (1.01–1.44)
Adjusted risk, epithelial tumors	HART, WHIT, HAR2, CHEN, and TZON	7.598 (4)	1.29 (1.02–1.63)

The authors demonstrated that “all meta-analyses arrive at relative risks greater than 1.0 with 95% confidence intervals excluding the null.” Despite these findings, the authors conclude that “existing evidence linking talc exposure to an increased risk of ovarian cancer cannot be viewed as scientifically conclusive”. A dose response relationship is not demonstrated. This study was supported by Johnson and Johnson. (Gross and Berg 1995).

Cramer et al, 1999

In 1999, Cramer et al (with Harlow as a coauthor) published a new case-control study of 563 epithelial ovarian cancers, including 86 serous borderline tumors. Controls were 523 women. No increased risk of ovarian cancer was seen in never users of powder vs non-genital powder users. For those who never used or had nongenital powder use vs any genital use, the odds ratio was 1.60 (95% CI 1.18-2.15) for development of ovarian cancer. Adjustments for age, community, parity, oral contraceptive use, BMI, and family history of breast or ovarian cancer were made.

These authors then did meta-analysis with the following results:

Risk of ovarian cancer with perineal exposure to talc from key epidemiologic studies.						Odds ratios and confidence			
Author	Cases Total n	Exposed (%)	Controls Total n	Exposed (%)	Crude OR (95% CI)	.1	.5	1	2
Cramer <i>et al.</i> (1982)	215	(42.8)	215	(28.4)	1.9 (1.3-2.8)				
Hartge <i>et al.</i> (1983)	135	(49.6)	171	(58.5)	0.7 (0.4-1.1)				
Whittemore <i>et al.</i> (1988)	188	(52.1)	539	(46.0)	1.3 (0.9-1.8)				
Harlow and Weiss (1989)	116	(42.2)	158	(40.5)	1.1 (0.7-1.7)				
Booth <i>et al.</i> (1989)	217	(65.0)	434	(59.0)	1.3 (0.9-1.8)				
Harlow <i>et al.</i> (1992)	235	(48.5)	239	(39.3)	1.4 (1.0-2.1)				
Rosenblatt <i>et al.</i> (1992)	77	(87.0)	46	(88.0)	1.0 (0.3-3.0)				
Chen <i>et al.</i> (1992)	112	(6.2)	224	(2.2)	2.9 (0.9-9.4)				
Tzonou <i>et al.</i> (1993)	189	(3.2)	200	(3.5)	0.9 (0.3-2.7)				
Purdie <i>et al.</i> (1995)	824	(56.7)	860	(52.0)	1.2 (1.0-1.5)				
Shushan <i>et al.</i> (1996)	200	(10.5)	408	(5.6)	2.0 (1.0-3.6)				
Cook <i>et al.</i> (1997)	313	(50.8)	422	(39.3)	1.6 (1.2-2.1)				
Chang and Rish (1997)	450	(44.0)	564	(35.6)	1.4 (1.1-1.8)				
Cramer <i>et al.</i> (1999)	563	(27.0)	528	(18.2)	1.7 (1.2-2.2)				
Summary odds ratio (95% confidence interval)					1.4 (1.2-1.5)				

Cramer *et al.* conclude that “a consistent association between talc and ovarian cancer appears unlikely to be explained by recall bias or confounding” (page 356). This study, too, was supported by a grant from the National Cancer Institute. (Cramer 1999).

Huncharek *et al.*, 2003

Sixteen case control studies (Booth, Beral, and Smith 1989; C.-J. Chang *et al.* 2017; Y. Chen *et al.* 1992; Cook, Kamb, and Weiss 1997; D. W. Cramer *et al.* 1982; D. W. Cramer 1999; Godard *et al.* 1998; Harlow and Weiss 1989; Ness *et al.* 2000; Purdie *et al.* 1995; Rosenblatt, Szklo, and Renshew 1992; Tzonou *et al.* 1993; Whittemore *et al.* 1988; Wong 1999) were found to be homogeneous and delivered 11,933 subjects (4959 cases). Pooled meta-analysis of ever perineal talcum powder use versus no exposure “yielded a summary relative risk of 1.33 with a 95% confidence interval of 1.16-1.45, a statistically significant result suggesting a 33% increased risk of developing ovarian cancer”. No dose response was found. However, the study did not collect the necessary data to permit this determination. Huncharek *et al.* spend the rest of the paper dismissing their result as NOT supporting an association between talc and ovarian cancer. According to the disclosure, this research was partially supported by the Marshfield Medical Research Foundation. There was no mention of financial support from Johnson & Johnson or Imerys (although disclosed in a 2007 paper by the same authors – Huncharek 2007).

Langseth et al 2008

The Langseth study drew data from The International Agency on Cancer Research (IARC) review of the literature, published as a Monograph in 2010 (which classified non-asbestiform talc as possibly carcinogenic)³, but did not provide a comprehensive report on this review or the findings. IARC was founded in 1965 and comprises investigators from 25 countries who “promote international collaboration in cancer research” (IARC.fr website). Langseth found an OR of 1.35 (95% CI 1.26-1.46), suggesting a statistically significant increase in ovarian cancer risk and concluded that “epidemiological evidence suggests that the use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. Langseth commented in the high degree of consistency in the studies reviewed and proposed that “the mechanism of carcinogenicity may be related to inflammation.”

See insert below.

³ IARC defines Group 2B as follows: Group 2B: The agent is possibly carcinogenic to humans. This category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data. (IARC 2012).

Langseth et al, 2008

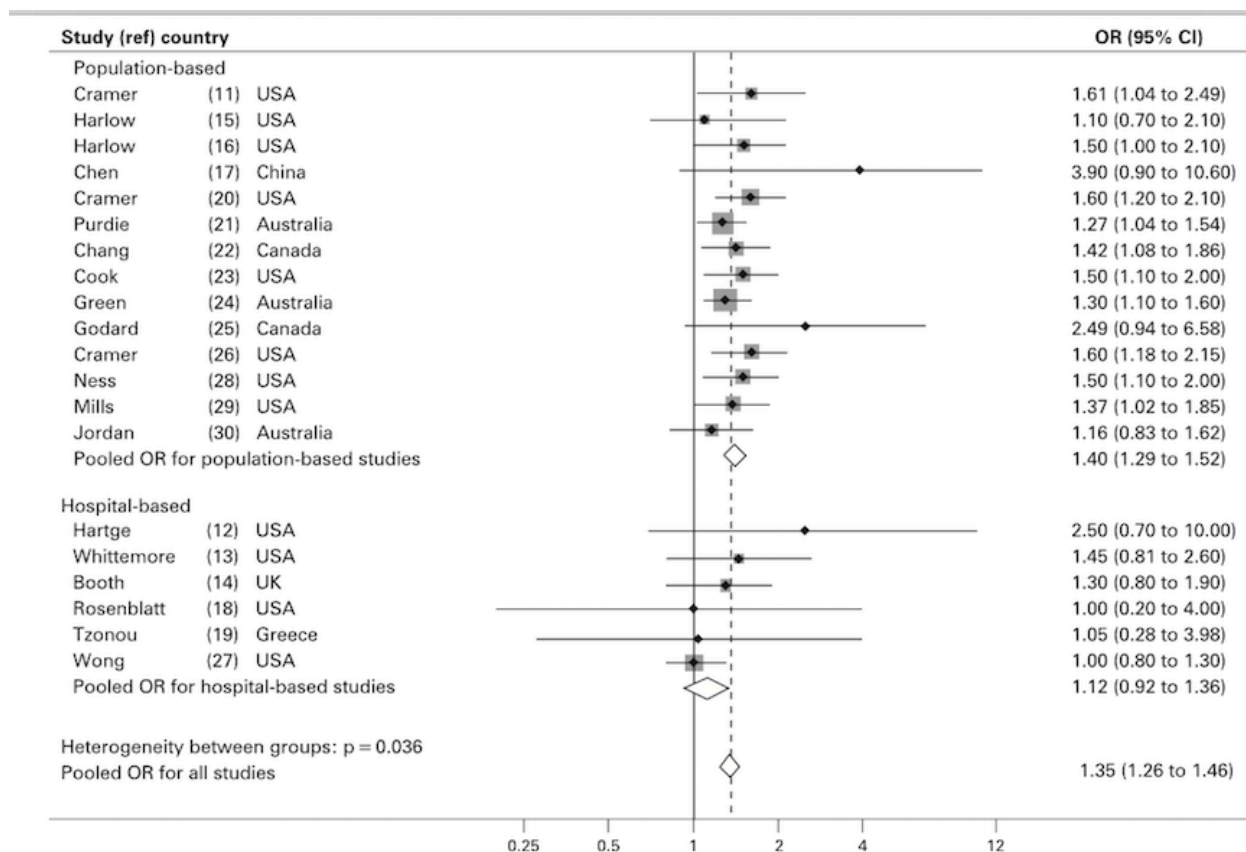


Figure 1 Results from case-control studies contributing data on perineal talc use and ovarian cancer. Results are presented as odds ratios (ORs) and their corresponding confidence intervals (95% CIs) and represented by squares and lines, respectively. Results are separated in 14 population-based and six hospital-based case-control studies. Pooled ORs for all population-based studies combined and all hospital-based studies combined are given OR pooling by fixed effect models (Mantel-Haenszel method).

11=Cramer et al, 1982

15=Harlow and Weiss, 1989

16=Harlow et al, 1992

17=Chen et al, 1992

20=Cramer and Xu, 1995

21=Purdie et al, 1995

22=Chang and Risch, 1997

23=Cook et al, 1997

24=Green et al, 1997

25=Godard et al, 1998

26=Cramer, 1999

28=Ness et al, 2000

29=Mills, et al, 2004

30=Jordan et al, 2007

12=Hartge et al, 1983

13=Whittemore et al, 1988

14=Booth et al, 1989

19=Tzonou et al, 1993

27=Wong et al, 1999

18=Rosenblatt et al, 1992

The Langseth et al study was financed by the Cancer Registry of Norway.

Terry et al, 2013

The Ovarian Cancer Association Consortium, an international, multidisciplinary group, investigates factors related to ovarian cancer development, including case-control studies and identification and analysis of genes associated with cancer risk. It is supported, in part, by the Ovarian Cancer Research Fund, the United States National Cancer Institute, and Cancer Research UK. Raw data from the following studies were pooled and analyzed: Rosenblatt et al, 2011 (including previously unpublished additional patients and data), Goodman et al, 2008 (previous unpublished data on powder use), Lo-Ciganic et al, 2012 (previously unpublished data on powder use), Moorman et al, 2009 (adding previously unpublished patients and data), Cramer et al, 1999 (with additional patient data), Pike et al, 2004 (previously unpublished powder use data), Merritt et al, 2008 (with additional patient data), and Chang et al, 1997 (including previously unreported patient data). Confounders adjusted for include age, oral contraceptive use and duration, parity, tubal ligation, BMI, race/ethnicity. The cases were 8525 cases of ovarian, fallopian tube, and primary peritoneal cancer, reflecting the recognition, in the decade of the 2000s, of the overlap and similarity and possible common etiology of these differently named cancers. In this study, 31% of cases used genital powder, as opposed to 25% of controls. Comparing ever users of genital powder with never users, the OR was 1.24 (95% CI 1.15-1.33). Similar results were seen for genital use vs non-genital use of powder. Risks were stronger for patient with BMI < 30. There was no association with parity, OC use, tubal ligation status, or menopausal status. Histologic break down of the cases showed significant increased risk in both borderline (OR 1.29 [95% CI 1.14-1.48]) and invasive cancers (OR 1.21, [95%CI 1.12-1.32]). Significant increased odds ratios with genital powder use were seen for invasive serous, endometrioid and clear cell tumors, but not invasive mucinous tumors. (Terry et al. 2013).

Penninkilampi and Eslick, 2017

The most recent meta-analysis is from two authors at the University of Sydney in New South Wales, Australia. The authors analyzed 24 case-control studies and 3 cohort studies on perineal talcum powder use and risk of development of ovarian study, excluding studies of fewer than 50 cases and duplicated published data. A total of 14,311 cases of ovarian cancer were included. Quality of the component studies were scored on the Newcastle-Ottawa Scale; none scored perfect, but the lowest score was 5/10, so none were excluded. Long term talcum powder use was judged greater than 10 years and was associated with an increase in ovarian cancer risk of OR=1.25 (95% confidence interval (CI) 1.10-1.43). (Lifetime applications of perineal talc of 3600 times roughly correlates with 10 years use; increased risk of ovarian cancer was found with fewer and more applications than 3600.) “Any perineal talc use was associated with any serous, serous invasive, serous borderline and endometrioid subtypes of ovarian cancer (Figure 2c).” This is the largest meta-analysis to date and continues to support the association of perineal talc use with increasing the risk of epithelial ovarian cancers. (Penninkilampi and Eslick 2018).

The Prospective Cohort Studies

There are three true prospective cohort studies looking at genital talcum powder use to perineum, diaphragms or menstrual pads or such use in some combination.

Gertig 2000

The Nurses' Health Study (Gertig et al, 2000) is a 20-year duration study (1976-1996) of 78,630 nurses age 30-55 (in 1976) in the USA. Perineal talcum powder use was first queried in 1982. The cohort answered questionnaires every other year. Ovarian cancer developed in 307 nurses. The relative risk (RR) for ever use of talcum powder and development of any epithelial ovarian cancer was 1.09 (95% CI 0.86-1.37). Invasive serous ovarian cancer demonstrated a statistically significant elevated multivariate RR of 1.40 (95% CI 1.02-1.9) (controlled for age, parity, duration of oral contraceptive use, BMI, tubal ligation, smoking and menopausal status). No other histologic group (all serous including borderline tumors, endometrioid or mucinous tumors) showed elevated risk with appropriate confidence intervals. Within this study there was no dose-response demonstrated, although P for trend was 0.5. For users over 45 years old in 1982 RR for serous ovarian cancer was 1.51 (95% CI 1.07-2.15). No such increased relative risk for any ovarian cancer type was seen for those under 45 in 1982. Gates (2010) continues the analysis of the NHS, finding no increased risk of any subtype. (Gertig et al. 2000).

Houghton 2014

The Women's Health Initiative Study was published by Houghton et al in 2014. This study of 61,576 postmenopausal women (age 50-79) showed ever-talc-use (perineal, diaphragm, pad) was not associated with statistically significant increased risk of development of any ovarian cancer contrasted to never-use (Hazard ratio=1.12 [95% CI 0.92-1.23]). There were 429 incident cases of ovarian cancer over the 12+ years of this study. In this study, talc use in any form was combined, no histologic information was obtained, and information on frequency of use was not obtained. (Houghton et al. 2014).

Gonzalez 2016

Gonzalez et al, 2016 studied a cohort of sisters or half-sisters of breast cancer patients in the USA. After exclusions, (BSO, missing data), 41,654 women were followed a median of 6.5 years during which 135 ovarian cancer, 5 fallopian tube cancers and 4 peritoneal cancers were diagnosed. Eight other cancers were likely from one of these three sites. (Only 96 cases of cancer were verified by medical record or death certificate review; all other were solely patient-reported at annual questionnaire responses.) At entry, the participants completed questionnaires regarding genital talc use as powders or spray and its frequency and douching. Perineal powder use was inversely associated with the development of ovarian-type cancer (Hazard ratio=0.73 (95% CI 0.42-1.1). Douching during the 12 months prior to study entry was associated with an increased risk of ovarian cancer (HR=1.8 [95% CI 1.2-2.8]), while combined talc and douching in the 12 months antecedent to study entry resulted in an HR=1.8 (95%CI 0.81-3.9). The authors acknowledge that they cannot know which powders contained talc and admit "powder has changed over time..." Additional limitations include small numbers, failure to ask questions about frequency or duration of powder usage, and short-term follow-up. With an expected latency period of over twenty years, this study would not pick up all cases. All of these deficiencies result in a failure to capture the true risk. (Gonzalez et al. 2016).

The Case-Control Studies

Cramer et al.'s landmark 1982 case control study looked at perineal talcum powder use in 215 white patients with epithelial ovarian cancer matched by age, race, and residence to 215

community women. These 215 cases included 39 borderline tumors. All pathology was histologically reviewed. Cases and controls were interviewed as to talc exposure from surgical glove, diaphragm use, and perineal use and/or dusting menstrual pads. Talc use varied between cases (42.8%) and controls (28.4%). Any perineal talc exposure showed an adjusted relative risk of ovarian cancer of 1.92 (95% confidence limits 1.27-2.89). (This relative risk was adjusted for parity and menopausal status.)

In the ensuing thirty-five years, at least 24 case-control studies looking at the association of talc and ovarian cancer, both invasive and borderline, have been published. Studies vary in design quality and size, but show a consistent increased risk of ovarian cancer with genital talcum powder use. That data summary follows and is attached as Exhibit B.

Based on the limitations of the cohort studies and the variances in design and size of the case-control studies, I based my opinions largely on the meta-analyses, particularly Penninkilampi's most recent study. In my opinion, meta-analysis provides the most reliable evidence in this situation. The large number of overall cases (>14,000) in this study improves the power to detect a relatively small effect size. The authors agree: "As it stands, a meta-analysis of observational studies, such as the present study provides the highest level of evidence practically feasible for this research question." (Penninkilampi and Eslick 2018).

In my opinion, meta-analysis is the most valid and reliable way to study an issue like ovarian cancer, that is relatively rare and requires a long study period to detect. The cohort studies were not designed to specifically to look at talcum powder. Instead, the use of talcum powder is only one of many queries. All of the cohort studies are limited by failure to obtain complete information, lack of power, selection bias, and short follow-up.

When looking at epidemiological studies with a critical eye and in their totality, they demonstrate a clear, consistent, and statistically significant increased risk of EOC (approximately 20-50%) with the genital use of talcum powder products. This risk is replicated over a large number of case-control studies, one cohort study, and all meta-analyses/pooled analyses over several decades. Recall and confounding bias in case-control studies appear to have minimal impact. (Penninkilampi and Eslick 2018; Langseth et al. 2008). There appears to be no significant publication bias. (Berge et al. 2017; Penninkilampi and Eslick 2018).

MECHANISM

How Talc Particles Reach the Tube, Ovary and Peritoneum

In 1971, Henderson, et al of Cardiff, Wales published their findings of talc deeply embedded in ovarian cancers. (Henderson et al. 1971)(Talc was also demonstrated in cervical cancers, endometrial cancers and non-diseased ovaries.) Ten years previously, Egli and Newton had demonstrated that carbon particles instilled in the posterior vaginal fornix would be "flushed" from the fallopian tubes removed transabdominally (No propulsive force of talc introduction was used in this study). (Egli and Newton 1961). Glove powder from vaginal examination can be found in the peritoneal cavity one to four days after exam. (Sjösten, Ellis, and Edelstam 2004). Based on the studies of Egli and others, Dr. J. Donald Woodruff began to postulate that "some agent enters the peritoneal cavity through the fallopian tube, irritates the pelvic peritoneum,

produces proliferation and with an added unknown ingredient results in the development of malignancy.” (Woodruff 1979). Dr. Woodruff emphatically encouraged more scientific attention to agents introduced into the vaginal canal. This paper is the text of a lecture delivered in October of 1978. Drs. Longo and Young expressed their concerns about talc and pathogenesis of ovarian cancer and also encouraged further study of the risks of cosmetic talc use in women. (D. L. Longo and Young 1979). Although I reviewed the small number of articles that dispute talcum powder’s ability to reach the tubes and ovaries, I rejected these claims. It is a universally accepted phenomenon by the gynecologic medical community, well documented in the scientific and medical literature, that the female genital tract functions as a conduit for foreign material to enter the peritoneal cavity. This is the process that occurs with talcum powder.

How Inflammation Leads to Mutagenesis and Cancer

“Prolonged chemical exposures, persistent foreign bodies, recurrent acute inflammation or certain pathogens are all causes of chronic inflammation.” (Ferguson, Chronic inflammation and mutagenesis, 2010). In this milieu, cytokines are generated, particularly TNF-alpha and IL-1beta. These cytokines generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS are incompletely reduced oxygen compounds that travel through the cell hungrily seeking electrons to steal or donate. These TNF-alpha radicals are potent mutagens and are comparable to the effects of ionizing radiation. (Yan et al. 2006; Yan, Peng, and Li 2009) (Yan methods described in 2009 book chapter). These ROS radicals cause DNA breaks, DNA adducts as well as having epigenetic effects (for example, lysine acetylation in chromosomal histones). The generation of TNF-alpha is DNA synthesis dependent and occurs in the macrophage (a WBC first responder in inflammation). (Liou and Storz 2010; Ferguson 2010; Yan 2011).

Inflammation and its involvement in the etiology and development of many types of cancer, has been studied extensively. (Klampfer 2011).

The inflammatory basis for cancer development is also supported by studies showing a reduced risk of cancer with the use of anti-inflammatory agents. (Burn et al. 2011).

This inflammatory cascade has been shown to occur in the pathogenesis of EOC as well. (Shan and Liu 2009; Saed, Morris, and Fletcher 2018; Saed, Diamond, and Fletcher 2017, 2017; Saed et al. 2018; Khan et al. 2011; Trabert et al. 2014).

In the “normal” cell, DNA damage is either repaired or the damaged cell is directed via the P53 pathway to apoptosis. Yan et al (2006) found more DNA aberrations in homozygous p53-negative cells of colon cancer origin. (Yan et al. 2006). Gates et al (2008) document absence of some DNA repair mechanisms in patients who are genital talc exposed compare to controls in New England Case Control Study as well as the Nurses’ Health Study. (Gates et al. 2008).

In an *in vitro* study by Shukla (2009), crocidolite asbestos and non-fibrous talc caused expression of different genes in mesothelial cells and ovarian epithelial cells producing inflammatory cytokines. (Shukla et al. 2009).

Buz’Zard transformed normal ovarian epithelial cells to malignant cells by talc exposure. (2007). (Buz’Zard and Lau 2007). Her methods are supported by the works of Yan et al and Khan et al.

Harper and Saed have recently reported a mechanism by which talc enhances the pro-oxidant state in normal [ovarian and tubal] and ovarian cancer cells, through inductions of gene point mutations (SNPs) in key oxidant enzymes, altering their activities. (Harper and Saed 2019).

Multiple investigators have looked at the effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of developing ovarian cancer. Although somewhat inconsistent, data regarding NSAID and aspirin use suggest a protective effect (results of these studies are inconsistent. (Murphy et al. 2012; Trabert et al. 2014, 2019). In a case control study, use of NSAIDs increased the risk of ovarian cancer. (A. H. Wu et al. 2009). Trabert et al pooled 12 population based case-control studies regular aspirin use decreased the risk of ovarian cancer, both low dose and high dose. Daily high dose NSAIDs decreased ovarian cancer risk. (Trabert et al. 2014). Trabert et al looked at 15 prospective cohort studies from North America and Europe and found no effect of aspirin or NSAIDs on ovarian cancer risks. (Trabert et al. 2019). No study found an effect on ovarian cancer of acetaminophen use, an analgesic, antipyretic with no anti-inflammatory properties. Dixon et al found no correlation with pre-diagnosis aspirin or NSAID use and survival duration after the diagnosis of ovarian cancer. (Dixon et al. 2017)

ASBESTOS AND OTHER CONSTITUENTS

There is evidence from medical literature that talcum powders are not pure talc, but contain impurities including asbestos. (Cralley, Key, et al. 1968; Cralley, Keenan, et al. 1968; Rohl et al. 1976; Werner 1982; Locky 1981; Paoletti et al. 1984; Blount 1991). I have also seen evidence of testing of Johnson and Johnson talcum powder products by Dr. William Longo demonstrating the presence of asbestos and fibrous talc in talcum powder product samples. (W. E. Longo and Rigler 2018). In addition, I have seen numerous Johnson and Johnson testing results showing the presence of asbestos in their talcum powder products. (Exhibit 28, Deposition of John Hopkins, Ph.D., MDL No. 2378, 2018; Exhibit 47, Deposition of Julie Pier, MDL No. 2738, 2018).

Asbestos is well known to be one of the most potent human carcinogens. The International Agency for Research in Cancer (IARC) has determined that asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. IARC 2012. According to IARC, all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite and talc containing asbestiform fibers (fibrous talc) are carcinogenic. The IARC Working Group found that a “causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive studies in women with heavy occupational exposure to asbestos. (Acheson et al. 1982; Wignall and Fox 1982; Germani et al. 1999; Berry, Newhouse, and Wagner 2000; Magnani et al. 2008; IARC 2012). The IARC 100C Working Group was convened in 2009, with results published in 2012.

In 2011, Camargo et al, published a meta-analysis of epidemiologic studies of ovarian cancer in asbestos exposed women. (Camargo et al. 2011). Their finding of a standardized mortality ratio (SMR) of 1.77 for risk of ovarian cancer mortality (95% confidence intervals 1.37-2.28) corroborate the finding of the IARC Working Group.

Distinction of peritoneal mesothelioma and ovarian carcinomatosis can be difficult. Even with such discrimination, asbestos increases ovarian cancer risk. (Alison Reid, Klerk, and Musk 2011).

“Consumer products are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure”. (IARC 2012). The mechanism of carcinogenesis of asbestos is the same as discussed above: induction of the inflammatory cascade resulting in mutagenesis either through a direct or indirect mechanism. Although migration/transport through the genital tract is the primary source of exposure with genital talcum powder use, inhalation represents a secondary exposure route. With either route, talcum powder particles can be also absorbed and transported through the lymphatics or blood system to pelvic organs and lymph nodes. The mechanism for the carcinogenicity of asbestos in the ovary and elsewhere provides a plausible biological mechanism by which it can contribute to the carcinogenicity of talcum powder products.

I have also seen evidence of the presence of heavy metals, including nickel, cadmium, and cobalt in Johnson and Johnson talcum powder products. (Exhibit 47, Deposition of Julie Pier, MDL 2738, 2018). Nickel and chromium are Group 1 carcinogens. (IARC 2012). Cobalt is identified by IARC as Group 2b possibly carcinogenic. (IARC 2012). The mechanism of action described by IARC, is inflammatory in nature. These heavy metals likely contribute to the carcinogenicity of talcum powder products by the inflammatory mechanism described at length in this report.

I have reviewed the list of fragrances chemicals contained in Johnson’s Baby Powder and Shower to Shower products and the expert report of Dr. Michael Crowley. I agree with Dr. Crowley’s opinion that these chemicals likely contribute to the inflammatory properties, toxicity and/or carcinogenicity of these products.

DETERMINATION OF CAUSATION

In 1965, epidemiologist Sir Austin Bradford Hill published his factors for determining causation from associations found in epidemiologic studies. (Hill 1965). These factors have been widely used, but are not considered absolute or required for a causal determination. These considerations have also been elaborated upon for the 21st century by Fedak et al. (Fedak et al. 2015). For a doctor treating patients, knowledge of risk factors and causes of diseases are important for diagnosis, prevention, and treatment of the diseases. In essence, risk factors (associated with a health outcome) can be considered causal when the biological and molecular mechanisms for this relationship are known or predictable based on scientific research. The following are the Bradford Hill considerations and my analysis as they relate to talcum powder products and their relationship with ovarian cancer.

Strength: There is no set magnitude or threshold for ascribing causality. I would maintain that any practice or element that increases the risk of ovarian cancer by ANY consistent percentage is significant. Ovarian cancer is, usually, a fatal disease, not a trivial inconvenience. The increased risk of ovarian cancer in perineal talc users in epidemiologic studies is 1.2-1.5, a 20-50% increased risk.

Consistency: The consistency of the case-control epidemiologic studies the uniformity of the meta-analyses (Harlow et al, 1992, Gross and Berg, 1995, Cramer et al 1999, Huncharek et al 2003, Langseth et al, 2008, the pooled study of Terry et al 2013, and the recent Penninkilampi 2017) is impressive. The studies are from different populations across three continents. The seeming inconsistency with the cohort studies are likely due to lack of power and other study design limitations. (Narod 2016). Strength and consistency are very important to a physician involved in patient care.

Specificity: Bradford Hill noted that different agents may cause more than one disease. Furthermore, any disease may have multiple component causes. “One-to-one relationships are not frequent”. (Hill 1965). Certainly, talc causes talcosis and medically induced pleural inflammation. The body of epidemiologic work supports talcum powder’s role in risk of epithelial ovarian cancer. For a physician, this consideration is less important than strength of association and consistency.

Temporality: This requirement is met by studies of risk of ovarian cancer for those who used talcum powder versus those who did not. It may take in vitro studies to establish threshold dose exposures. Bradford Hill did not address latency which is another marker of temporality. In the case of talcum powder use and ovarian cancer, the average latency period exceeds twenty years. (Magnani et al. 2008; A. Reid et al. 2014; Okada 2007). Reverse temporality is most unlikely in this case. Temporality is not particularly important to a physician as long as it has been shown to exist.

Biologic gradient: This refers to dose response relationship which is not seen in all of the epidemiologic studies, but is demonstrated in some. (Harlow et al. 1992; S. Chang and Risch 1997; Daniel W. Cramer et al. 2016; Schildkraut et al. 2016; Terry et al. 2013; Penninkilampi and Eslick 2018). In the studies that failed to demonstrate a clear dose response, many simply did not have adequate data to assess. With genital talcum powder use, quantifying exposure is challenging in terms of measuring the exact amount used in each application, the amounts that migrate or are transported through the genital tract, the amount inhaled, and the amount absorbed through the vaginal mucosa. It is also impossible to measure how much of each constituent is present in any application. In vitro studies would help clarify dose response relationships and mechanisms. To a physician, dose response can be helpful when determining causality, but not essential.

Plausibility: The growing body of evidence from in vitro studies enhance the plausibility of talcum powder’s role in the causation of ovarian cancer. The talcum powder reaches the tubes, ovaries, and peritoneum by migration/transport of particles as described earlier in this report. Once there, these particles create a hostile inflammatory environment of reactive oxygen and reactive nitrogen species capable of causing mutagenesis/carcinogenesis. This general mechanism is not only plausible, but accepted widely - even though the details at the molecular level are still being clarified. I placed a great deal of importance on the mechanism consideration and I find it compelling.

Coherence: As Bradford Hill stated, assessing causation “should not seriously conflict with the generally known facts of natural history and biology of disease”. (Hill 1965). This consideration has been satisfied, since talcum powder and its causal relationship with ovarian cancer is compatible with our knowledge of cancer and cancer processes.

Experiment: Sir Bradford Hill discussed this point as an experimental change in the epidemiologic milieu which mitigated the statistical finding. Fedak et al interpret this point in a more contemporary way: biochemical, in vitro experiments and laboratory investigation of genetic and epigenetic pathways. (Fedak et al. 2015). In this context, there is a growing body of evidence to support the biologic, genetic and epigenetic consequences to the ovarian epithelial cell with talcum powder exposure. (Shukla et al. 2009; Fletcher, Nicole, Memaj, Ira, and Saed, Ghassan 2018; Saed, Morris, and Fletcher 2018; Buz’Zard and Lau 2007).

Analogy: Sir Bradford Hill suggested the analogy of rubella and thalidomide causing birth defects in a similar fashion. I would suggest the analogy of asbestos causing ovarian cancer and mesothelioma or HPV causing cervical cancer.

I give precedence to strength of association and consistency as most important factors. If these are met, I judge plausibility and experiment next in importance.

Cornstarch as a safer alternative

Talc has been known to be more inflammatory and toxic than starch products for decades. (Eberl and George 1948). In addition, there is no epidemiological evidence linking cornstarch to ovarian cancer. (S. Chang and Risch 1997; Daniel W. Cramer et al. 2015; Cook, Kamb, and Weiss 1997). Whysner and Mohan reviewed the literature regarding talc and cornstarch and their relationship to epithelial ovarian cancer. The authors concluded that: 1) due to the chemical nature of cornstarch, a biological mechanism by which cornstarch could cause ovarian cancer is implausible; 2) epidemiologic studies have found no association between cornstarch and ovarian cancer; and 3) no increased risk of ovarian cancer from perineal cornstarch use is predicted. (Whysner and Mohan 2000).

Conclusions

In my opinion, talcum powder products cause epithelial ovarian cancer. This opinion is based on my assessment of the totality of the epidemiologic data presented in the medical and scientific literature, the biologic mechanism, and the credible presence of known carcinogens in the products. This assessment was made by analyzing and weighing the extensive evidence in the context of Bradford Hill considerations.

Summary of my opinions:

1. Johnson and Johnson talcum powder products cause the development and progression of epithelial ovarian cancer.
2. There is credible evidence that Johnson and Johnson baby powder products contain asbestos. Asbestos and fibrous talc cause epithelial ovarian cancer. Heavy metals and

fragrance chemicals added to the products can also contribute to the carcinogenicity of Johnson & Johnson Baby Powder and Shower to Shower products.

3. Talc and asbestos create an inflammatory pro-carcinogenic environment in the human body, the mechanism for epithelial ovarian cancer development and progression.
4. Perineal application of talcum powder products results in the tubal and intraperitoneal deposition of talc and asbestos by migration and transport through the genital tract. Inhalation is a secondary route of exposure.

I reserve the right to amend or modify the report as new information becomes available.

I have not testified in litigation over the previous 4 years. I am charging \$600 per hour for my work on this matter. Additional materials I considered are attached as Exhibit C.

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Exhibit A

CURRICULUM VITAE
Ellen Blair Smith, M.D.

PERSONAL DATA:

Birth Date: December 9, 1951

Mailing Address: 2311 Camino Alto Road
Austin, Texas, USA 78746

Email: ellenblairsmith@gmail.com

NPI: 15583054

Employment Status: Retired from Texas Oncology, PA December 31, 2015
Medical director, Halcyon Home Hospice, April, 2017-present

EDUCATIONAL HISTORY:

1969: Diploma, Grimsley High School, Greensboro, North Carolina
1971: A.A. , St. Mary's Junior College, Raleigh, North Carolina
1973: B.A. Biology, University of North Carolina, Greensboro. North Carolina
1977: M.D., University of North Carolina. Chapel Hill, North Carolina

SCHOLASTIC HONORS:

1974 Mosby Award
1976 Merck Award
1976 Student Aptitude Award, North Carolina Society of Obstetrics and
Gynecology
1976 Alpha Omega Alpha, University of North Carolina School of Medicine
1977 American Medical Women's Association Citation of Scholastic
Achievement

POSTGRADUATE TRAINING:

1977-1978: Internship, Obstetrics and Gynecology, UTHSCSA, San Antonio, Texas
1978-1981: Residency, Obstetrics and Gynecology, UTHSCSA, San Antonio, Texas
1979: Galloway Fellowship, Memorial Sloan-Kettering, NY, NY
1981-1984: Fellowship, Gynecologic Oncology, Duke University Medical School,
Durham, NC (1983: American Cancer Society Fellow)

PREVIOUS EMPLOYMENT:

1984-1987: Assistant Professor, Gynecologic Oncology, University of Virginia Medical
School, Charlottesville, Virginia
1987-1989: Physician and Sole Proprietor, Gynecologic Oncology, Austin, Texas
1989-1995: Physician and President, Austin Gynecologic Oncology Associates, Austin, TX

CURRICULUM VITAE
Ellen Blair Smith, M.D.

1995-2008: Physician and Partner, Southwest Regional Cancer Center, Austin, Texas
2008-2015: Physician Shareholder, Texas Oncology, Austin, Texas

MEDICAL LICENSURE:

Texas Medical Board: F0313 (active)
DEA: AS 1121021 (active)
Texas DPS 40063099 (active)
North Carolina State: 24537 (inactive)
Virginia State: 10103669 (inactive)

BOARD CERTIFICATIONS:

1985 American Board of Obstetrics and Gynecology (lifetime certified, voluntary
recertification 1996)
1987 American Board of Obstetrics and Gynecology, Division of Gynecologic Oncology
(lifetime certified, voluntary recertification 1996)
2011 Hospice and Palliative Medicine (via ABOG), expires 2021

APPOINTMENTS:

1981-1982 Associate, Obstetrics and Gynecology, Duke University Medical School,
Durham, NC
1982-1984 Assistant Professor, Obstetrics and Gynecology, Duke University Medical
School, Durham, NC
1984-1987 Assistant Professor, Department of Obstetric and Gynecology, University
of Virginia Medical Center, Charlottesville, VA
1997-2000 Renaissance Women's Center Advisory Board, Austin, Texas
1998-2003 Hospice Austin Medical Advisory Board, Austin, Texas
1999-2001 Mediation Committee, Travis County Medical Society, Austin, Texas
2001-2007 Gynecologic Cancer Foundation, Board of Directors
Nominating Committee Chair 2004
2007-2008 Section Chief Ob-Gyn, Seton Medical Center, Austin, Texas
2007-2014 Member Surgical Committee, Seton Medical Center, Austin, Texas
2011-2013 Medical Director of Surgical Services, US Oncology (elected office)
2011-2013 Member, National Policy Board Executive Committee, US Oncology
2011-2015 Member, Managed Care Committee, US Oncology
2011-2015 Member, Pathways Committee, US Oncology

PROFESSIONAL SOCIETIES:

Alpha Omega Alpha (1976-current)
American Cancer Society
1985-1987 Charlottesville-Albemarle Unit
Board of Directors
Executive Committee

1984-1986 Virginia Unit

CURRICULUM VITAE

Ellen Blair Smith, M.D.

Board of Directors
Colorectal Cancer Control Project Steering Committee
Finance Committee 1986
Nominating Committee 1986
1987-1988 Austin, Texas Unit
Public Education Chairman
American Congress of Obstetrics and Gynecology (1988-Life Member)
Society of Gynecologic Oncology (1988-lifetime)
Program Committee 1995-1996
Coding Committee 1996-2001
Nominating Committee 2008
Palliative Care Committee 2009-current
Session Moderator-Palliative Care- SGO Annual Meeting-2014
Steering Committee, SGO Genetics Summit-2015
American Academy of Hospice and Palliative Medicine 2010-present

PUBLICATIONS (PEER-REVIEWED JOURNALS) :

Smith, EB, Weed, JC, Tyrey, L and Hamond, CB: "Treatment of Nonmetastatic GTD: Results of Methotrexate-Folinic Acid." *Amer J Obstet Gynecol*, 144:88, 1982.

Smith, EB, Szulman, AE, Hinshaw, W, Tyrey, Surti, U, and Hammond, CB: "Human Chorionic Gonadotropin Level in Complete and Partial Hydatidiform Moles and Nonmolar Abortuses." *Amer J Obstet Gynecol*, 149: 129, 1984.

Smith, EB, Clarke-Pearson, DL, and Creasman, WT: "A VP-16 and Cis-Platinum Containing Regimen for Treatment of Refractory Ovarian Germ Cell Malignancies" *Amer J Obstet Gynecol*, 150:927, 1984.

Smith, EB, Dunnick, R, Nelson, PA and Hammond, CB: "Renal Metastases of Malignant Gestational Trophoblastic Disease with Particular Attention to the Use of Intravenous Urography in Staging." *Gynecol Oncol* 20: 137, 1985.

Barter, J, **Smith, EB**, Szpak, CA, et al: "Leiomyosarcoma of the Uterus: A Clinicopathologic Study of 21 Patients." *Gynecol Oncol* 21:221, 1985.

Puleo, JG, Clarke-Pearson, DL, **Smith, EB**, Barnard, DE, and Creasman, WT: "Superior Vena Cava Syndrome Associated with Gynecologic Malignancy." *Gynecol Oncol* 23:59, 1986.

Taylor, PT, Anderson, WA, Barber, SR, Covell, JL, **Smith, EB**, and Underwood, PB: "The Screening Papanicolaou Smear: Contribution of the Endocervical Brush." *Obstet Gynecol* 70:734, 1987.

Anderson, WA, Found, D, Peters, W, **Smith, EB**, Bagley, C and Taylor, PT: "Platinum-Based Combination Chemotherapy for Malignant Mixed Mesodermal Tumors of the Ovary." *Gynecol Oncol* 32: 319, 1989.

Plante, M, **Smith, EB** et al: "The case of a viable pregnancy post vaginal radical trachelectomy followed by combined chemoradiation." *Gynecol Oncol* 123:421, 2011.

CURRICULUM VITAE
Ellen Blair Smith, M.D.

PUBLICATIONS (INVITED ARTICLES AND BOOK CHAPTERS):

Creasman, WT, **Smith, EB** and Clarke-Pearson, DL: "Gestational Trophoblastic Disease." *The Female Patient*, 9:66, 1984.

Smith, EB, Clarke-Pearson, DL, and Creasman, WT: "Screening of Cervical Cancer." (Chapter10) *Screening and Monitoring of Cancer*. Basil A Still, ed. John Wiley & Sons; 1985.

Smith, EB and Creasman, WT: "Preinvasive and Invasive Cervical Carcinoma Associated With Pregnancy." *Principles of Medical Therapy in Pregnancy*. N Gleicher, ed. Plenum Publishing Corp. New York, New York. 1985. Revision 1990.

Smith, EB, Hammond, CB, Gore, H and Hertig, A. "Gestational Trophoblastic Disease". *Management of the Patient with Cancer*. 3rd edition. TF Nealon, ed. W. B. Saunders CO, Philadelphia, Pa. 1986.

Smith, EB: "Gynecology for the Urologist." *Adult and Pediatric Urology*. J Gillenwater. ed. Year Book Medical Publishers; 1987. Revision 1991.

INVITED LECTURES:

SGO State of the Art Meeting 2011- Palliative Care

SGO Winter Meeting 2013-Palliative Care

Exhibit B

EXHIBIT A

First author and year	Cases (%talc use)	Controls (%talc use)	OR	95% CI	Dose Response	Comments
Cramer, 1982	215 (43%)	215 (28%)	1.9	1.27-2.89		
Hartge,1983	135	171	0.7	0.4-1.1		hosp, letter only. Only 10 with perineal use
Whittemore, 1988	188 (52%)	539 (46%)	1.45	0.81-2.8	no	perineal use, mixed hosp and population
Harlow, 1989	116	158	2.8	1.111.7	no	LMP only, deodorant powder +/-talc
Booth,1989	235 (68%)	451 (61%)	rare=0.9 weekly=2.0 daily=1.3	0.3-2.4 1.3-3.4 0.8-1.9	no	hosp. path reviewed
Rosenblatt, 1992	77 (91%)	46	1	0.2-4.0		These nmbers are way too small.
Chen,1992	112 (6%)	224 (2%)	3.9	0.9-11.6		also used occupational exposure, only 7 vs 5 total perineal powder users
Harlow, 1002	235 (48.5%)	239 (39.3)	1.5	1.0-21	trend NSS	perineal use
Tzounou,1993	189 (3%)	200 (3.5%)	1.05	0.28-3.98		hosp, hairdye, low usage numbers, Greece
Purdie,1995	824 (57%)	860 (52%)	1.25	1,04-1,54		adj for parity , 17% LMP Austrailia
Shusan, 1996	200 (11%)	406 (5.6%)	seems to be : simple X2= 0.4			Never/seldom vs mod-a lot, Focus on fertility drugs Israel
Chang, 1997	450 (44%)	564 (35.6%)	all 1.42 LMP 1.24 inv 1.51	1.08-1.86 0.76-2.02 1.13-2.02	duration=borderline frequency=no	no assn with cornstarch, Canada
Cook, 1997	313	422	1.5	1.1-2.0	no	ever powder use, looked at genital deodorant as well
Godard,1998	170 (10.6)	170 (4.7)	2.49	0.94-6.56		perineal use only p=0.066 French Canadians
Wong, 1999	499 (47.8%)	755 (44.9%)	genital+pad 1.1 genital 1.0 pad 0.9	0.7-1.7 0.8-1.3 0.4-2.0	no	

first author, year	cases (% talc use)	controls (%talc use)	OR	95% CI	dose-response	Comments
Cramer, 1999	563 (45%)	523 (36%)	any genital powder 1.6 perineal talc 1.69	1.18-2.15 1.26-2.27	no	
Ness,2000	767 (55%)	1367 (47%)	genital 1.5 pad 1.6	1.1-2.0 1.1-2.3	no	BTL protective, risk increased witalc on all areas body
Mills,2004	256 (43%)	1122 (37%)	ever talc 1.37 serous 1.77	1.02-1.85 1.12-1.81	no	
Merritt, 2008	1576 (46%)	1509 (43%)	1.17	1.01-1.36		adjusted OR, decreased with ASA, BIG NUMBERS Australia includes LMP, FT, PP
Moorman,2009	143 AA 943 white	189 AA 868 white	1.19 1.04	0.68-2.09 0.82-1.33)		
Rosenblatt, 2011	812	1313	all 1.27 LMP 1.55 inv 1.38	0.97-1.66 1.02-2.37 0.77-2.47	no	
Kurtha, 2012	902 (22%)	1802 (20.9%)	1.4	1.16-1.69		The definitive fertility drug risk paper
Wu, 2015	hispanics 308 (38%) AA 128 (48%) white 1265 (41%)	380 (28%) 143 (44%) 1868 (30%)	1.56 1.77 1.41	0.8-3.04 1.20-2.62 1.21-1.67		Stat sig more talc use in Aas
Cramer, 2016	2014 (51%)	2100 (48%)	1.33	1.16-1.52	trend for freq none for duration	
Schildkraut,2016	584 (63%)	745 (53%)	1.44	1.11-1.86	yes	

Exhibit C

- “A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis.” *British Journal of Diseases of the Chest* 73 (1979): 285–88. [https://doi.org/10.1016/0007-0971\(79\)90054-8](https://doi.org/10.1016/0007-0971(79)90054-8).
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- . "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 27, no. 3 (2018): 248–57. <https://doi.org/10.1097/CEJ.0000000000000340>.
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Exhibit 12

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
DANIEL L. CLARKE-PEARSON, MD**

A handwritten signature in cursive script that reads "Dan Clarke-Pearson MD".

Date: November 16, 2018

Daniel L. Clarke-Pearson, MD

Daniel L. Clarke-Pearson, MD
Robert A. Ross Distinguished Professor and Chair
Department of Obstetrics and Gynecology
University of North Carolina, Chapel Hill

Background and Qualifications

I am certified by the American Board of Obstetrics and Gynecology as a specialist in obstetrics and gynecology as well as a subspecialist in gynecologic oncology. The focus of my clinical practice, teaching and research for the past 40 years has been the care of women with gynecologic cancers (cancers of the ovary, fallopian tube, uterus, cervix, vagina, and vulva). In addition, I also provide care for complex gynecologic surgical problems (endometriosis, large ovarian tumors, leiomyomata).

I received a BA from Harvard College (major in biology). I spent a year as a laboratory technician developing a device to noninvasively detect deep venous thrombosis. I then attended medical school at Case Western Reserve University School of Medicine (Cleveland, OH). After graduating in 1975, I completed a four-year residency in Obstetrics and Gynecology at Duke University Medical Center (Durham, NC). I then completed a three-year fellowship in Gynecologic Oncology at Duke. From 1982-1985 I was an assistant professor on the Duke faculty (Division of Gynecologic Oncology). From 1985-1987 I was the Director of Gynecology and Gynecologic Oncology at the University of Illinois (Chicago, IL). I returned to Duke in 1987 to serve as the Director of Gynecologic Oncology and Director of the Gynecologic Oncology Fellowship program. I was appointed a full professor with tenure and was awarded a Distinguished Professorship (James Ingram Professor of Gynecologic Oncology) in 1993.

In 2005, I was appointed Chair of the Department of Obstetrics and Gynecology at the University of North Carolina (Chapel Hill, NC). As the Robert A. Ross Distinguished Professor and Chair, I have administrative responsibilities over 75 faculty, 28 residents in obstetrics and gynecology and 29 fellows receiving subspecialty training in eight subspecialties. I have continued to provide clinical care to women with gynecologic cancers including surgery, administration of chemotherapy, conducting clinical trials and educating residents in Obstetrics and Gynecology and Fellows in Gynecologic Oncology.

I have published over 200 peer-reviewed manuscripts in the medical literature. I have also written over 50 chapters for medical textbooks and edited three medical textbooks. My research has focused on the treatment of gynecologic cancers, surgical techniques, and the prevention of venous thromboembolic (VTE) disease. I have conducted the practice defining clinical trials evaluating various methods to prevent VTE in gynecologic surgery. I have served on the editorial boards of two peer-review journals (*Obstetrics and Gynecology* and *Gynecologic Oncology*). I served as a board examiner for the American Board of Obstetrics and Gynecology for eighteen years.

I have been actively involved with relevant medical organizations including the American College of Obstetricians and Gynecologists (ACOG), the Society of Gynecologic Oncology (SGO), the American College of Surgeons (ACS) and the Gynecologic Oncology Group (GOG). I have lead numerous postgraduate continuing education courses sponsored by ACOG. Most have focused on teaching obstetricians and gynecologists complex pelvic surgery and management (and prevention) of surgical complications. I have served on several ACOG committees (Technical Bulletins, Gynecologic Management and Grievance) and was the chair of the Gynecologic Management Committee that wrote Clinical Opinions distributed to ACOG members. I also served a three-year term on the ACOG Executive Board. As a gynecologic oncologist, I have been an active member of the SGO and have served on a number of SGO Committees and the Executive Board. In 2010, I was the SGO President. As a member of the American College of Surgeons, I have presented CME lectures at the ACS annual meeting and have served on the ACS Obstetrics and Gynecology Advisory Committee. I am currently a member of the ACS Commission on Cancer. The GOG is a cooperative group organization sponsored by the National Cancer Institute to conduct clinical trials investigating new treatments to improve the outcomes of women with gynecologic cancers. Many of the publications on my CV (Exhibit A) derive from participation in these clinical trials.

Currently, I am a member of the SGO Ethics Committee and the President of the Council of University Chairs of Ob Gyn (CUCOG).

Materials and Methods

I was asked to provide opinions on these questions: 1) Can the use of talcum powder in the perineal area cause epithelial ovarian cancer? and 2) If so, what is the biological mechanism for this occurrence?

To answer these questions and prepare this report, I sought to obtain relevant information through several sources. I primarily relied on a PubMed search of “talc AND Ovarian Cancer”, “Ovarian Cancer AND risk factors”, “Talcum Powder AND Ovarian Cancer”, “Talcum Powder AND Cancer”, “Talc AND Cancer”, “Asbestos AND Ovarian Cancer”, “Asbestos AND Cancer”. These searches provided peer-reviewed papers that included original research, case-controlled studies, cohort studies, meta-analysis studies, and review papers and systematic analysis. I also searched some of the references cited in these papers. Google searches were also performed. I also reviewed a number of textbooks searching for “ovarian cancer risk factors” and “talc/talcum powder”. In addition to my literature review, I received relevant materials at my request to clarify a particular topic or answer a question. I approached this research with the same scientific rigor that I would use in my own clinical, academic, and research practice.

I assessed the data and conclusions of these peer-reviewed articles considering the strengths and weaknesses of each particular study. The medical and scientific literature on these topics varies in the quality of the study design and, at times, in conclusions. I approached each article objectively and critically, assessing for factors such as design, power, reputation of author(s),

quality of journal, and potential biases. The increased risk associated with the genital use of talcum powder is consistently described over decades. When formulating my opinions regarding causality, I considered the extensive body of literature in its totality, weighing the data and information according to its importance using the concepts outlined by Bradford Hill. Overall, I believe that the opinions expressed in this report are strongly supported by credible scientific research.

Overview of Ovarian Cancer

Approximately 22,000 women in the US will be diagnosed with ovarian cancer annually. To date, there is no method to screen for ovarian cancer and symptoms associated with ovarian cancer are vague and not specific. Therefore, at the time of initial diagnosis, nearly 75% of women will have ovarian cancer spread throughout the abdominal cavity and into the lung (pleural effusion). Current treatment includes initial surgery to attempt to remove the bulk of the cancer (“debulking surgery”) followed by treatment with multi-agent chemotherapy. Unfortunately, the majority of women will ultimately die from this malignancy. The most common histologic type of ovarian cancer is high-grade serous cancer, also termed “epithelial ovarian cancer” (EOC).

Pathogenesis of Ovarian Cancer

There are several theories as to the origin of ovarian cancer. One holds that “incessant ovulation” requires “repair” of the ovarian surface epithelium after each ovulation. The “repair” mechanism is prone to generate DNA errors (mutations) that result in malignant transformation. (Fathalla 1971). This theory is supported by observations that events that reduce ovulation are associated with a lower risk of a woman developing ovarian cancer. (Pregnancy, breast feeding, use of oral contraceptives all reduce the risk of ovarian cancer). (Havrilesky et al. 2013; La Vecchia 2017).

Before 2008, it was presumed two other cancers in women (fallopian tube and primary peritoneal) were distinct from ovarian cancer. However, Levanon recognized that many EOCs actually arise in the fallopian tube and metastasize to the ovary and peritoneal cavity. (Levanon, Crum, and Drapkin 2008). This observation is supported by molecular data (especially the frequent finding of P53 mutations in the fallopian tube and EOC metastases. (Fathalla 2013; Kurman and Shih 2016; Dubeau and Drapkin 2013; Chien et al. 2015). Today, we believe that EOC, fallopian tube carcinoma and primary peritoneal carcinoma are the same entity and share similar risk factors and pathogenesis.

By definition, cancer results from gene mutations in normal cells that transform the normal cell into a cell that has lost its regulation of controlled growth. Mutations can occur through a number of processes. Some mutations may be inherited from either the patient’s mother or father. BRCA1, BRCA 2 and mismatch repair gene (Lynch Syndrome) mutations are such examples. In most instances, the mutations occur due to exposures such as virus (HPV virus causing cervix, anal, vulvar and oropharyngeal cancers), tobacco smoking (lung cancer) and

exposure to x-rays (leukemia). Some exposures result in a chronic inflammatory response that induces mutations as the normal cell attempts to repair damage such as that caused by asbestos (pulmonary mesothelioma, ovarian cancer). These mutations can also occur spontaneously as cells (and individuals) age. (Bottazzi, Riboli, and Mantovani 2018).

Inflammation and Cancer

There is a clear link between inflammation (resulting in oxidative stress) and cancer risk. This is true for many types of cancer including ovarian cancer. (Balkwill and Mantovani 2001; Coussens and Werb 2002; Okada 2007; Reuter et al. 2010; Crusz and Balkwill 2015; Fernandes 2015). Inflammation causes cancer through promoting cell proliferation, oxidative stress, and DNA damage and gene mutations. This process is associated with many steps in the genesis of cancers including initiation, progression, metastases and chemoresistance. Both inflammatory cells and cancers produce cytokines and chemokines that contribute to cancer growth and spread. Cytokines, particularly TNF-alpha and IL 1 beta, generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). These are potent mutagens and are comparable to the cell damage caused by ionizing radiation (Yan, 2006). These ROS radicals cause DNA breaks and DNA adducts. The inflammation cascade has been shown to occur in the pathogenesis of EOC. (Shan and Liu 2009; Saed, Diamond, and Fletcher 2017; Khan et al. 2011; Saed et al. 2018; Trabert et al. 2014). Harper and Saed recently reported the induction of single nucleotide polymorphisms (SNPs) following exposure of normal ovarian and tubal cells and ovarian cancer cells to talcum powder. (Harper and Saed 2019). In a "normal cell", DNA damage may be repaired. Alternately, the damaged cell may undergo "programmed cell death" (apoptosis) as directed by the P53 pathway. (P53 is a tumor suppressor gene).

Talcum powder is known to elicit an inflammatory response in animal and humans. (Eberl and George 1948; Radic et al. 1988; "NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3Fl Mice (Inhalation Studies)" 1993). Shukla demonstrated in vitro that crocidolite asbestos and non-fibrous talc caused expression of genes in ovarian epithelial cells producing inflammatory cytokines. (Shukla et al. 2009). Gates documented absence of some DNA repair mechanisms in patients who were genital talcum powder exposed when compared to controls in the New England Case Control Study. (Gates et al. 2008). In another series of in vitro experiments, Buz'Zard transformed normal ovarian epithelial cells to malignant cells by talc exposure. (Buz'Zard and Lau 2007). Yan and Kahn have demonstrated similar findings in their laboratories. (Yan et al. 2006; Khan et al. 2011).

EOC Risk Factors

Inherited mutations such as BRCA1, BRCA 2 are the most significant risk factor. The lifetime risk of developing ovarian cancer is 39-46% in BRCA1 carriers and 11-27% in women with BRCA 2 mutation. (Ring et al. 2017). This is compared to 1.3% lifetime risk in non-carriers. However, BRCA mutations only account for 10-15% of all EOC (Lancaster 2015). Women with hereditary

risk are also affected by genetic modifiers, including nongenetic and environmental factors. (Levy-Lahad 2007). In addition to talcum powder use and asbestos, other risk factors include increasing age, family history of ovarian or breast cancer, nulliparity, early menarche or late menopause, high fat diet, infertility, endometriosis, polycystic ovarian syndrome, hormone replacement therapy, IUD use, history of pelvic inflammatory disease and obesity. (Hunn and Rodriguez 2012; Mallen, Townsend, and Tworoger 2018; Park et al. 2018; Folkins et al. 2018).

Multiparity, breast feeding, oral contraceptive use, tubal ligation, salpingoophorectomy, and hysterectomy (without salpingoophorectomy) reduce the risk of developing EOC. (Hunn and Rodriguez 2012; Mallen, Townsend, and Tworoger 2018; Park et al. 2018; Folkins et al. 2018).

Talcum Powder, Asbestos and other carcinogens

During my postgraduate (residency) training (1975-1979) in obstetrics and gynecology it was reported that asbestos had been identified in ovarian cancer tissue samples (Henderson) and that talcum powder contained asbestos. It seemed plausible that asbestos (a known carcinogen) could be an EOC risk factor. However, we were taught that asbestos had been removed from talcum powder in the production process.

As a young gynecologic oncologist, it was reassuring to learn that asbestos was no longer contained in talcum powder because we knew that asbestos was a potent carcinogen. IARC monograph 100c (2012) clearly summarizes the evidence associating asbestos to cancer of the lung, larynx and ovary. Experimental models demonstrate sufficient evidence for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) and that all forms, as well as talc containing asbestiform fibers are carcinogenic to humans. Specifically addressing the increased risk of EOC in women exposed to asbestos in occupational settings, there are at least five cohort mortality studies (Acheson et al. 1982; Wignall and Fox 1982; Germani et al. 1999; Berry, Newhouse, and Wagner 2000; Magnani et al. 2008), two population-based cohort studies (Vasama-Neuvonen et al. 1999; Pukkala et al. 2009) and a case control study (Langseth and Kjaerheim 2004) showing a causal association between exposure to asbestos and ovarian cancer.

In the late 1970s concerns that talc could be associated with EOC were expressed by Woodruff and Longo. (Woodruff 1979). The hypothesis suggested that talc applied to the perineum (vulva) ascends to the vagina and then into the uterus and through the fallopian tubes to implant on the ovary and other peritoneal surfaces. This foreign body was known to create a potent inflammatory reaction when found in the lungs, pleural cavity and peritoneal cavity. In fact, as gynecologic surgeons, we were taught to wash the talcum powder off of our surgical gloves before opening the abdomen to prevent inflammatory reactions and adhesions.

In 1982 a case-control study was the first epidemiologic study alerting the medical community of the possible association of talc use and EOC. (D. W. Cramer et al. 1982). Cramer compared women who did and did not use talc in their perineal hygiene. Regular use of talc was found to be associated with an increased occurrence of EOC by 92% (OR of 1.92. 95% confidence

interval 1.27-2.89). Cramer wrote, "It is not clear whether this derives from the asbestos content of talc or from the uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates."

Talcum powder also contains other carcinogens including asbestos, talc containing asbestiform fibers (fibrous talc), heavy metals such as nickel, chromium and cobalt (possible 2b), and other inflammatory agents, toxins, and carcinogens contained in the fragrance chemicals in talcum powder. (Expert Report of Longo and Rigler 2018; Exhibit 28, Deposition of John Hopkins, Ph.D., MDL No. 2378, 2018; Exhibit 47, Deposition of Julie Pier, MDL 2738, 2018; Expert Report of Michael Crowley, Ph.D, MDL No. 2738, 2018).

Epidemiology Studies

The association of talcum powder and EOC is based on several types of epidemiologic studies. Of course, a randomized controlled double-blinded trial would be more conclusive. However, a randomized trial would be unethical given the evidence that talcum powder causes EOC.

When looking at these epidemiologic studies in their totality, the data shows a consistent, statistically significant increased risk of developing EOC with perineal talcum powder use. Overall, the risk is increased 20-60% when compared with women who did not use talcum powder.

The original case control study published by Cramer et al in 1982 evaluated the use of perineal talcum powder in 215 white women with EOC (29 cases were "borderline" or ovarian cancer of low malignant potential). These women with EOC were matched by race, age and residence to 215 women in the same community. Talc exposure from surgical gloves, diaphragm use and perineal use was ascertained. Talc was used by 42.8% of women with EOC and only 28.4% of women who did not have EOC. Any perineal talc exposure showed a 1.92-increased relative risk of EOC (95% confidence limits 1.27-2.89). (D. W. Cramer et al. 1982).

Subsequently, there have been at least 24 other case-control studies looking at the association of talc and EOC. Overall, the case-control studies show a 30-40% increased risk of EOC associated with talcum powder use. These individual studies vary in size and quality and I weighted them accordingly. Three recent case-control studies replicated previous studies showing an increased risk of EOC in women using perineal talcum powder. Wu evaluated 1701 Californian women with EOC and found talc significantly increased the risk of EOC by 40% in whites, 20% in Hispanics and 56% in African Americans. (Wu et al. 2015). Owing to the small number of African American women in this study, the findings were not significant. Subsequently, the National Cancer Institute sponsored a multi-center study of African American women and found a 44% increase in EOC associated with talc use. A dose-response was also found for duration of use and number of lifetime applications ($p < .05$). (Schildkraut et al. 2016). Cramer performed a case control study (with additional pooled data) in 2016 that included nearly 4,000 women with EOC finding an elevated EOC risk of 33% (OR 1.33; CI....). Risk increased with frequency and duration of use. (Cramer et al. 2016).

While recent case-control studies and cohort studies are compelling, I feel that meta-analysis studies are much stronger in that they include larger numbers of patients resulting in greater statistical power. I reviewed six meta-analyses reported between 1995 and 2018. All of these studies report a statistically significant increase risk of EOC in women who use perineal talc:

Author	Years	# case control studies	Odds Ratio	95% Confidence interval
Gross & Berg	1995	9	1.27	1.09-1.48
Cramer	1999	14	1.36	
Huncharek	2003	16/11,933 subjects	1.33	1.16-1.45
Langseth	2008	14	1.40	1.29-1.52
Terry	2013	8/8,525 cases	1.24	1.15-1.33
Penninkilampi	2018	24/13,421 cases	1.31	1.24-1.39

Penninkilampi reported that there was a further increase in EOC in women who used talcum powder more frequently. In those women who had greater than 3,600 lifetime applications the odds ratio increased to 1.42 (OR 1.42; CI 1.25-1.39) when compared with women who used < 3,600 applications (OR 1.32; CI 1.15-1.50). In this study, talcum powder use was associated with an increased incidence of endometrioid and serous EOC but not mucinous or clear cell types. (Penninkilampi and Eslick 2018).

In summary, when evaluating all epidemiological studies, there is a consistent and statistically significant increased risk of developing EOC with perineal talcum powder use.

Migration

How is it possible for cosmetic talcum powder, applied to the perineum, to reach the fallopian tube and ovary and cause an inflammatory response that could result in malignant transformation?

As compared to males, the female reproductive tract is open and allows migration of potential pathogens into the peritoneal cavity. The female reproductive tract is in continuity between the peritoneal cavity and the external environment. For example, an ovum extruded from the ovary (an intraperitoneal organ) can progress down the fallopian tube to the uterine cavity, implant and result in a pregnancy that delivers vaginally. The converse is also obvious. It is clearly recognized that sperm (including sperm and sperm particles which would be non-motile) ascend from the vagina through the uterus and into the fallopian tube and into the peritoneal cavity. (Jones and Lopez 2006). Sexually transmitted bacterial infections (for example, gonorrhea and chlamydia) ascend from the vagina to the tube and ovary resulting in pelvic inflammatory disease and tubo-ovarian abscesses. While sperm and bacteria are “motile”, non-motile substances have been demonstrated to ascend from the vagina to the peritoneal cavity. As far back as 1961, Egli demonstrated that carbon particles placed in the posterior vaginal

fornix were observed in the fallopian tubes within less than one hour in two of three patients tested. (Egli and Newton 1961). Venter and Iturralde placed albumin microspheres labelled with 99mTc into the vagina. (Venter and Iturralde 1979). During pelvic surgery the following day, radioactive levels were found in the tubes and ovaries in nine of 14 cases. Sjosten conducted a trial that showed that powder on gloves use to perform a gynecologic exam resulted in powder detected in the peritoneal fluid, tubes and ovaries one day after the examination. (Sjösten, Ellis, and Edelstam 2004). Likewise, talc has been detected on the ovaries following surgical oophorectomy. (Henderson et al. 1971; Heller, Gordon, et al. 1996; Heller, Westhoff, et al. 1996).

I reviewed the small body of literature suggesting that migration of particles does not occur and do not think these studies are compelling.

I believe that ascension of talcum powder and its constituents through the genital tract is the most important route of exposure. However, inhalation is another plausible mechanism. (IARC 2012; Steiling et al. 2018). With either route, at least some of the talcum powder components are likely to be absorbed into the lymphatic system and bloodstream, representing another mechanism for exposure to internal organs.

In my opinion, genital application of talcum powder is a significant risk factor for all users and can cause epithelial ovarian cancer in some women by an accepted mechanism. As an academic and practicing physician, I made this determination in the context of Bradford Hill considerations as follow:

Strength and consistency: This opinion is supported by overwhelming epidemiologic evidence showing that the use of talcum powder statistically increases a woman's risk of developing EOC by approximately 30 percent (Odds ratio 1.31; Penninkilampi 2018). Every meta-analysis before 2018 also reported similar increase in the risk of developing EOC with the use of talcum powder. In my view, especially when considering the severity and frequency of ovarian cancer and the preventable nature of talcum powder usage, this finding is critically important and consistently supported by numerous studies.

Specificity: Based on the epidemiologic studies cited in this report, there appears to be a specific ovarian cancer caused by talcum powder: epithelial ovarian cancer (EOC). This association satisfies this consideration, although I did not weigh this factor to be as important as strength and consistency.

Temporality: In many cancers where there are identified etiologic agents (smoking and lung cancer, HPV infection and cervical cancer) there is a latency period (time from exposure to the onset of the cancer) that can extend over decades. In the case of talcum powder and ovarian cancer there is a clear latency period of decades of talcum powder use before a woman develops ovarian cancer, thus fulfilling this consideration.

Biologic Gradient/Dose-response: Measuring the “dose” of talcum powder used by an individual woman is difficult to ascertain and has been dependent on recall by the woman. In general, studies have attempted to capture the application “frequency” (daily? Only used on perineal pads during menstrual cycle?) or duration of use (how many years?). In addition, biologic gradient or dose-response is not always linear (e.g. asbestos exposure and mesothelioma is generally thought to have a “threshold response”). None the less, a number of studies have demonstrated an association between “dose” and the occurrence of EOC (response). (Terry et al. 2013; Schildkraut et al. 2016; Daniel W. Cramer et al. 2016; Penninkilampi and Eslick 2018). In modern times, molecular research is often used to elucidate this factor. I anticipate that this will occur as more in vitro studies are performed with talcum powder.

Plausibility: This is obviously a critical factor when forming opinions on causation of a risk factor. Evidence shows that talcum powder ascends from the perineum through the vagina, cervix and uterus into the fallopian tubes and onto the ovary. Talcum powder is known to be an agent that causes inflammation. An inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis. Talcum powder causes ovarian cancer through this mechanism. The “agent(s)” that causes the inflammatory reaction and carcinogenesis may be talc, asbestos, fibrous talc, heavy metals and/or chemicals contained in fragrances added to talcum powder.

Coherence: Epidemiological data, in vitro and in vivo research are consistent in explaining the pathogenesis of EOC through the inflammatory mechanisms described above. (Saed, Diamond, and Fletcher 2017; Nadler and Zurbenko 2014). Further, this is consistent with the causes of other cancers.

Experiment: There are no randomized trials comparing outcomes of women who use or who do not use talcum powder in their perineal hygiene. Further, such a trial at this point in time would be unethical. How could we expose women to talcum powder when the existing evidence supports causation of EOC? Laboratory research (in vitro) present evidence to support the biologic, genetic and epigenetic consequence to ovarian epithelium when exposed to talcum powder. (Shukla et al. 2009; Fletcher and Saed 2018; Saed et al. 2018).

Analogy: There are numerous reports in the medical literature of minerals similar to talc causing cancer. Probably the most significant example is asbestos and lung cancer (mesothelioma).

Summary of Opinions

It is my opinion, based on research that I have conducted in the medical and scientific literature as well as my knowledge and experience as an obstetrician-gynecologist and as a subspecialist in gynecologic oncology for over 40 years, that the use of talcum powder products including Johnson’s Baby Powder and Shower to Shower, applied to the perineum of women, is a causative factor in the development of EOC. The mechanism by which talcum powder causes

cancer involves: 1) ascension of particles to the fallopian tubes and ovaries and 2) initiation of an inflammatory process that includes oxidative stress and specific genetic mutations.

These opinions are made to a reasonable degree of medical and scientific certainty.

I am being compensated for my work in this case at a rate of \$700 per hour.

I reserve the right to supplement or amend this report if new information becomes available.

The materials I considered are attached as Exhibit B. My prior testimony is attached as Exhibit C.

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Exhibit A

**UNC SCHOOL OF MEDICINE
CURRICULUM VITAE**

Personal Information

Name: Daniel Lyle Clarke-Pearson, M.D.

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Education and Training

Fellow	Duke University Medical Center	1979-1981	Gynecology Oncology
Residency	Duke University Medical Center	1975-1979	Obstetrics and Gynecology
Medical Degree	Case Western Reserve University School of Medicine	1971-1975	Medicine
Bachelor of Arts	Harvard College	1966-1970	Biology

Professional Experience

Active Consulting Staff	The Outer Banks Hospital	Oct 2009 – present	Medicine/Oncology Section
Chairman	University of North Carolina at Chapel Hill School of Medicine	September 2005 - present	Obstetrics and Gynecology
Robert A. Ross Distinguished Professor	University of North Carolina at Chapel Hill School of Medicine	September 2005 - present	Obstetrics and Gynecology
James M. Ingram Professor of Gynecologic Oncology	Duke University Medical Center	July 1993-2005	Gynecologic Oncology
Division Director	Duke University Medical Center	July 1987-2005	Gynecologic Oncology
Professor	Duke University Medical Center	July 1987-2005	Obstetrics and Gynecology

Director of Gynecology and Gynecologic Oncology	University of Illinois at Chicago	January 1985-1986	Obstetrics and Gynecology
Associate Professor	University of Illinois at Chicago	July 1984-1986	Obstetrics and Gynecology
Director of Gynecologic Oncology	University of Illinois at Chicago	July 1984-1985	Obstetrics and Gynecology
Associate Professor	Duke University Medical Center	January 1984	Obstetrics and Gynecology
Co-Director, Trophoblastic Disease Center	Duke University Medical Center	July 1982-1984	Obstetrics and Gynecology
Assistant Professor	Duke University Medical Center	July 1980-1984	Obstetrics and Gynecology

Honors and Awards

2009-2010	President, Society of Gynecologic Oncologists
2001-2013	America's Top Doctors for Women (176 Physicians): Women's Health
2008	CREOG National Faculty Award for Excellence in Resident Education
2004	Invited Panel Member, International Consensus Conference of the Prevention of Venous Thromboembolism, Windsor, England
2002	ACOG Roy Pitkin/Elsevier Award: One of top four papers published annually in <u>Obstetrics and Gynecology</u>
2001	America's Top Doctors for Women: Women's Health
1991	Invited Panel Participant, Consensus Meeting on the Prevention of Thromboembolism - Windsor, England
1985	Clinical Research Prize Paper – ACOG District Meeting
1981-1984	Junior Faculty Clinical Fellowship – American Cancer Society
1982	Donald F. Richardson Memorial Prize Paper -Best research paper presented by a Junior Fellow at a District ACOG Meeting
1981	Clinical Research Paper, Second Place ACOG Annual Clinical Meeting
1981	Junior Fellow First Prize Paper – ACOG District IV
1980	American Cancer Society Clinical Fellow

1979

Junior Fellow First Prize Paper – ACOG District IV

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Original Research

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 9. Omura GA, Blessing J, Vaccarello L, Berman M, Mutch D, **Clarke-Pearson D**, Anderson B: A randomized trial of cisplatin versus cisplatin + mitolactol (CM) versus cisplatin + ifosfamide (CIFX) in advanced squamous carcinoma of the cervix (SCC) by the Gynecologic Oncology Group (GOG). Presented at the 1995 American Society of Clinical Oncology Annual Meeting.
 10. **Clarke-Pearson DL**, Berchuck A, Kohler M, Rodriguez GC: Retroperitoneal drains/morbidity of nodes. Society of Gynecologic Oncologists, 1993.
 11. Hoskins WJ, McGuire WP, Brady MS, Copeland L, Homesley HD, **Clarke-Pearson DL**: Serum CA-125 for prediction of progression in advanced epithelial ovarian carcinoma (AOC). The Gynecologic Oncology Group (GOG). Proc ASOC (Abstract #707) 11:223, March 1992.
 12. McGuire WP, Hoskins WJ, Brady MF, Homesley HD, **Clarke-Pearson DL**: A Phase III trial of dose intensive (DI) cisplatin (CDDP) and Cytosan (CTX) in advanced ovarian cancer (AOC). Proc ASCO, March 1992.
 13. Hoskins WJ, McGuire WP, Brady MS, Homesley HD, **Clarke-Pearson DL**: Serum CA-125 for prediction in advanced epithelial ovarian cancer (AOC). The Gynecologic Oncology Group (GOG). Third Meeting of the International Gynecologic Cancer Society, September 22-26, 1991, Cairns, Australia.
 14. McGuire WP, Hoskins WJ, Brady MS, Homesley HD, **Clarke-Pearson DL**: A Phase II trial of dose intense (DI) versus standard dose (SD) Cisplatin (CDDP) and Cytosan (CTX) in advanced ovarian cancer (AOC). The Gynecologic Oncology Group (GOG). Third Meeting of the International Gynecologic Cancer Society, September 22-26, 1991, Cairns, Australia.

15. Shpall E, **Clarke-Pearson DL**, Soper JT, Berchuck A, Jones R, Bast R, Lider Y, Vanacek K, Tyler T, Peters W: High dose alkylating agent chemotherapy with autologous bone marrow support in patients with Stage III/IV epithelial ovarian cancer. Society of Gynecologic Oncologists, 1990.
16. Soisson AP, Soper JT, Berchuck A, Creasman WT, **Clarke-Pearson DL**: The role of radiation therapy following radical hysterectomy for carcinoma of the cervix. Society of Gynecologic Oncologists, 1989.
17. Berchuck A, Soisson AP, Soper JT, **Clarke-Pearson DL**, McCarty KS Jr, Bast RC Jr: Cellular expression of CA-125 and metastatic potential of endometrial adenocarcinoma. Society of Gynecologic Oncologists, 1989.
18. Soisson AP, Berchuck A, Soper JT, **Clarke-Pearson DL**, Flowers J, Kinney R, McCarty KS Jr, Bast RC Jr: TAG-72 expression in benign and malignant endometrium. American College of Obstetricians and Gynecologists, Armed Forces District Meeting, 1988.
19. Christensen C, McCarty KS Jr, Flowers J, Soper JT, McCarty KS Sr, **Clarke-Pearson DL**: Progesterone receptor in ovarian carcinoma: Comparison of biochemical and immunohistochemical techniques. American College of Obstetricians and Gynecologists, Annual Clinical Meeting, 1988.
20. Genkins SM, Sotsman HD, Spritzer CE, Herfkens RJ, Carroll BA, Kadir S, **Clarke-Pearson DL**, Coleman RE: Diagnosis of deep venous thrombosis: Comparison of venography with four noninvasive techniques. The Radiological Society of North America, 1988.
21. Mutch DG, Soper JT, Babcock CJ, Christensen CW, **Clarke-Pearson DL**, Hammond CB: Recurrent gestational neoplasia: Experience of the Southeastern Trophoblastic Disease Center. Abstract, Gynecol Oncol 29:133, 1988.
22. Christensen C, McCarty KS Jr, Flowers J, Soper JT, McCarty KS Sr, **Clarke-Pearson DL**: Analysis of estrogen receptor in ovarian carcinoma using biochemical and monoclonal antibody assays. Presented at American College of Obstetricians and Gynecologists District IV Meeting. Atlanta, Georgia, October 1987.
23. **Clarke-Pearson DL**, Creasman WT: Prevention of postoperative deep venous thrombosis by two intense low-dose heparin regimens: A controlled trial. Abstract, Society of Pelvic Surgeons, 1986.
24. **Clarke-Pearson DL**, DeLong ER, Synan IS, Coleman RE, Creasman WT: Variables associated with postoperative deep venous thrombosis. Abstract, Society of Gynecologic Investigation, p. 119, 1986.
25. Siegel RS, Kessler CM, **Clarke-Pearson DL**, Barth S, Fortune W, Reba R, Coleman RE: Application of Indium-111-labeled donor platelets to detection of deep venous thrombosis. Clin Res 32:323A, 1984.
26. Creasman WT, Henderson D, **Clarke-Pearson DL**: Use of estrogens after treatment for adenocarcinoma of the endometrium. Gynecol Oncol 17:2, p. 255, 1984.
27. Siegel RS, **Clarke-Pearson DL**, Barth S, Fortune W, Lewis RJ, Reba R, Coleman RE: Application of Indium-111-labeled donor platelets to detection of deep venous thrombosis and monitoring clot resolution on streptokinase therapy. Blood, Suppl 62:310, 1983.
28. Siegel RS, **Clarke-Pearson DL**, Coleman RE: Indium-111-labeled platelets in the detection of deep venous thrombosis and pulmonary embolism. Blood 50:223, 1982.

29. Postoperative thromboembolism prophylaxis in gynecologic oncology: A prospective, controlled trial of low-dose heparin and external pneumatic calf compression. *Gynecol Oncol*, 1982.

Un-refereed Publications

1. **Clarke-Pearson DL**. Prevention and Management of Venous Thromboembolism (15 minute Video) for the Globathon to End Women's Cancer. September 2014.
2. **Clarke-Pearson DL, Brincat C, Tang J**. Prevention and Management of Venous Thromboembolism in Gynecologic Surgery. *ACOG Update*. Vol 37, No 2. August, 2011.
3. **Clarke-Pearson DL**. Preventing Venous Thromboembolism: Evidence-based Perioperative tactics. *OBG Management*. 2006, 18:56-66.
4. **Clarke-Pearson DL**: Prevention of venous thrombosis following gynecologic surgery in menopausal patients. *Menopausal Medicine* Vol 4 (4):6-9, 1996.
5. Rodriguez GC, **Clarke-Pearson DL**: What is the appropriate preoperative and prenatal screen for hemostatic disorders? *Obstet Gynecol Forum*, November 1991.
6. **Clarke-Pearson DL**, Hume RF: Venous thromboembolic disease in obstetrics and gynecology: Prevention, diagnosis and treatment. *Curr Problems in Obstet Gynecol*, 1989.
7. Hunter VJ, Christensen C, **Clarke-Pearson DL**: Evaluation and management of the abnormal Papanicolaou smear. *North Carolina Family Physician*, 1989.
8. **Clarke-Pearson DL**, Krumholz AB: When the pap smear is equivocal. *Patient Care* 23:43-47, 1989.
9. **Clarke-Pearson D**, DiSaia P, Mastroianni L, Richart R, Weingold AB: Advances in managing endometrial carcinoma. *Patient Care* 22:102-116, 1988.
10. Creasman WT, Smith EB, **Clarke-Pearson DL**: Current concepts of gestational trophoblastic disease. *Female Patient*, 1984.
11. Creasman WT, **Clarke-Pearson DL**: Abnormal cervical cytology: Spotting it, treating it. *Contemporary Obstet Gynecol* 21:53-76, 1983.
12. Hammond CB, **Clarke-Pearson DL**, Soper JT: Management of patients with gestational trophoblastic neoplasia: Experience of the Southeastern Regional Center. In: *The Proceedings of the World Congress on Gestational Trophoblastic Neoplasia*, Nigeria, 1982.
13. **Clarke-Pearson DL**: Application of impedance phlebography in obstetrics. Symposium on Noninvasive Diagnostic Techniques in Vascular Disease. San Diego, California, 1979.
14. **Clarke-Pearson DL**: The O.S.R. as an influence to health education. *The Scalpel*, Journal of Alpha Delta Alpha Medical Honor Society, 1975.

Teaching Record

2018

Visiting Professor, University of West Virginia, Morganton, WV

Antonio Palladino Lectureship

2016 Plenary Session, Society of Pelvic Surgeons, St Louis, Mo. “Venous Thromboembolism in

- Minimally Invasive Compared with Open Hysterectomy for Endometrial Cancer”
- Key Note Speaker. ACOG Armed Forces District Meeting, Orlando, FL
- Visiting Professor and Research Day Judge, Cleveland Clinic Department of Obstetrics and Gynecology and Women’s Research Institute, Cleveland, Ohio
- Visiting Professor, Department of Obstetrics and Gynecology, Carilion Roanoke Memorial Hospital, Roanoke, Va.
- 2015** Visiting Professor
University of Michigan
- 2014** Visiting Professor
Massachusetts General Hospital, ObGyn Department Grand Rounds
Boston, MA
Invited speaker: ACOG District II Annual Meeting, New York City
“Uterine Morcellation: A Decision Analysis”
- 2013** Visiting Professor and Resident Research Day Judge
Department of Obstetrics and Gynecology, University of Nebraska
Omaha, NE
Visiting Professor, Emory University Department of Obstetrics and Gynecology
Atlanta, GA
- Key Note Speaker: Inaugural Ireland Ovarian Cancer Forum
“Surgery for Ovarian Cancer”
Dublin, Ireland
Panel Moderator, American College of Surgeons Annual Clinical Congress
“General Surgery in the Pregnant Patient”
Washington, DC
- 2012** Clifford Wheelless Lecture, Johns Hopkins University, Department of Obstetrics and Gynecology, Baltimore, MD
- Panel Moderator, American College of Surgeons Annual Clinical Congress
“Multidisciplinary approach to Vaginal Fistula”
Chicago, IL
- Resident Research Day Judge and Visiting Professor
Department of Obstetrics and Gynecology, Greenville Hospital System, Greenville, SC
- Visiting Professor: University Teaching Hospital, Department of Obstetrics and Gynecology, Lusaka, Zambia
Cervical Cancer management
Current Treatment of Vulvar Carcinoma
Visiting Professor: Center for Infectious Disease Research in Zambia (CIDRZ), Lusaka, Zambia
Human Papilloma Vaccine for the Prevention of Cervical Cancer
- Visiting Professor: Inova Fairfax Hospital Women’s Center, Fairfax VA
- Visiting Professor: Emory University School of Medicine, Department of Obstetrics and Gynecology. Atlanta, GA
- 2011** Sloane Symposium: Current Issues and Controversies in Obstetrics and Gynecology
Columbia University, College of Physicians and Surgeons, Department of Obstetrics and

Gynecology

Vandewiele Lecturer: "Prevention of Venous Thromboembolism in Gynecologic Surgery"

Guest Lecturer and Judge: Resident Research Day, Columbia University
"What to say in your Operative Note"

University of Kentucky: Residents' Research Day Speaker

Virginia Commonwealth University School of Medicine
Department of Obstetrics and Gynecology Annual Ware-Dunn Symposium
Keynote speaker

2010 New England Obstetrical and Gynecological Society, Sturbridge, MA
Invited Speaker

ACOG Annual Clinical Meeting, San Francisco, CA
Luncheon Seminar Leader

George Washington University Medical Oncology Review Course
Washington, DC
Invited Faculty

MD Anderson Cancer Center Medical Oncology Review Course
Houston, TX
Invited Faculty

The Society of Gynecologic Oncology of Canada
Royal College of Physicians and Surgeons of Canada
Annual Meeting
Invited Lecturer: Thromboprophylaxis in Minimally Invasive Surgery

Visiting Professor
University of South Florida, Tampa, FL
Resident Research Day

2009 ACOG District IV Meeting, Asheville, NC
"Prevention of Venous Thromboembolism"
"Stump the Professors: Panel"

American College of Surgeons' Annual Meeting, Chicago, IL
"Complicated Hysterectomy"

Visiting Professor: Hartford Hospital, Hartford CT

Visiting Professor: University of Connecticut, Farmington, CT

Visiting Professor: Memorial Sloan Kettering Cancer Center

Southern Obstetric and Gynecologic Seminar, Asheville, NC
"Prevention of VTE following Gynecologic Surgery"
"The Operative Note: What to say?"

Woman's Hospital 7th Annual Founders Commemorative Lectureship, Woman's Hospital, Baton Rouge, LA

2008 Visiting Professor, Department of Obstetrics and Gynecology, Yale University

Course Director, ACOG CME Course “Complex Pelvic Surgery”, Phoenix, AZ

Invited Speaker: First Annual Gynecologic Cancer Symposium, Washington, DC April 18, 2008

Visiting Professor, University of Wisconsin Resident’s Research Day, Ben M. Peckman Memorial Lecturer, Madison, WI

ACOG representative to Symposium on Surveillance for Venous Thrombosis, American Society of Hematology, Washington DC

2007 Visiting Professor, Department of Obstetrics and Gynecology, University of Miami

Faculty, University of Utah CME Course “Obstetrics and Gynecology: Update and Current Controversies” Park City Utah

Visiting Professor, Department of Obstetrics and Gynecology St. Louis University, St. Louis MO

Invited Lecturer: Marvin Camel Memorial Lecture, Washington University, Department of Obstetrics and Gynecology, St Louis, MO

Presidential Panel Speaker: Society of Pelvic Surgeons Annual Meeting, Cleveland, OH “What Can We do to prevent Venous Thromboembolism?”

2006 Course Director: ACOG Annual Clinical Meeting: “Complex Gynecologic Surgery, Washington DC

Invited Speaker, ACOG District IV Annual Meeting, Palm Beach, FL

2005 Course Director: ACOG Annual Clinical Meeting: “Complex Gynecologic Surgery, San Francisco

Course Director: ACOG Free-standing CME Course “Complex Gynecologic Surgery, Preventing Complications” Dana Point, CA

2004 Society of Surgical Oncology: Symposium on Prevention of Venous Thromboembolism in the Surgical Oncology Patient

Postgraduate Course Faculty: ACOG Cancun, Mexico “Advanced Gynecologic Surgery”

American College of Obstetricians and Gynecologists, Annual Clinical Meeting, Philadelphia, PA
Faculty, 120 Course: Special Topics for the Advanced Gynecologic Surgeon
Faculty, Luncheon Seminar: “Prevention of Postoperative Venous Thromboembolism”
Speaker: “Late-breaking News in Gynecologic Oncology”

Visiting Professor, University of Kansas School of Medicine, Truman Medical Center

Faculty: ACOG Indiana Section Meeting, Indianapolis
“Surgery in the Obese Patient”, “Surgical Instruments”

2003 Faculty, The 3rd Annual Cancer Conference, Aultman Cancer Center, Canton Ohio
“Prevention and Management of Perioperative Venous Thromboembolism in the Gynecologic Cancer Patient”

Visiting Professor, Department of Obstetrics and Gynecology, University of Massachusetts, Worcester, MA

- 2002** Visiting Professor
Bowman Gray School of Medicine
- Residents' Day Research Judge
Winston Salem, NC
- American College of Surgeons' Annual Clinical Congress
Panel Discussant: "Surgical Problems: Unexpected adnexal mass, tuboovarian abscess"
Video Presentation: "Intraoperative Radiation Therapy for the treatment of Recurrent Cervical Carcinoma"
Discussant: Video Presentation "Laparoscopic Infrarenal paraaortic lymphadenectomy"
- 2001** ACOG Annual Meeting
Postgraduate Seminar
Gynecologic Surgery in the Elderly
- Visiting Professor
University of West Virginia, Faculty, Cancer Center Annual Symposium
"Chemosensitization and Radiation Therapy in the treatment of locally advanced cervical carcinoma."
- 2000** Keynote Speaker
Knoxville Obstetrical and Gynecological Society
- ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon
- Visiting Professor
East Carolina University School of Medicine
- Visiting Professor
Pennsylvania State University School of Medicine (Hershey)
- George Washington University
Medical Oncology Board Review Course (Faculty)
- 1999** ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon
- George Washington University School of Medicine
Medical Oncology Board Review Course (Faculty)
- Visiting Professor
University of Virginia Health Sciences Center
- ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon
- 1998** ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon

George Washington University School of Medicine
Medical Oncology Board Review Course (Faculty)

Visiting Professor
Temple University School of Medicine

Keynote Speaker
Maryland Obstetrical and Gynecological Society

Visiting Professor
University of Louisville
“Prevention of Postoperative Venous Thromboembolism”
“Management of Patients with Thrombophilias”

1997 Visiting Professor
University of Utah, Salt Lake City

ACOG Annual Meeting (Course Director)
Postgraduate Course
Advanced Surgery for the Gynecologist

Visiting Professor
Cleveland Clinic Foundation
Department of Obstetrics and Gynecology
Cleveland, Ohio

George Washington University School of Medicine
Medical Oncology Board Review Course (Faculty)

Keynote Speaker
Chicago Gynecological Society

Visiting Professor
University of Louisville School of Medicine

Visiting Professor
Washington University School of Medicine

Visiting Professor
Johns Hopkins University School of Medicine

ACOG Annual Clinical Meeting
Faculty, 120 Course: Special Topics for the Advanced Gynecologic Surgeon
Faculty, Seminar: “Gynecologic Surgery in the Elderly”
Faculty, Luncheon Seminar: “Prevention of Postoperative Venous Thromboembolism”

American College of Surgeons’ Annual Clinical Congress
Panel Discussant: “Management of Gynecologic Problems Encountered by the General Surgeon at the time of Surgery. “Surgical Management of Ovarian Cancer Discovered at the time of Laparotomy”

1996 Visiting Professor
Dartmouth Medical School

Director ACOG Postgraduate Course
Annual Clinical Meeting

Special Problems for the Advanced Gynecologic Surgeon

Visiting Professor
University of Tennessee School of Medicine
Chattanooga, Tennessee

Visiting Professor
University of South Florida School of Medicine
Tampa, Florida

Visiting Professor
Washington University School of Medicine
St. Louis, Missouri

John L. McKelvey Lecturer
New Treatments for Ovarian Cancer
University of Minnesota
Minneapolis, Minnesota

Faculty - Taubman Ovarian Cancer Symposium
St. Joseph's Hospital
Tulsa, Oklahoma

ACOG Postgraduate Course (Course Director)
San Juan, Puerto Rico
Advanced Pelvic Surgery

1994 ACOG Clinical Meeting CME Course
Orlando, FL
"Gynecologic Cancer"

Guest Speaker
Seattle Gynecological Society Assembly

1993 Visiting Professor - Department of OB/GYN
University of Massachusetts
Worcester, Massachusetts

ACOG Clinical Meeting - CME Course
Washington, DC
"Gynecologic Surgery"

PostGraduate Course in Obstetrics and Gynecology
Kaiser-Permanente - Maui, Hawaii
"Screening for Ovarian Cancer"
"Management of CIN with LEEP"
"Difficult Vaginal Hysterectomy"
"Incisions and Wound Closures"

Duke/US Surgical Course
"Laparoscopic Assisted Difficult Hysterectomy"

Visiting Professor - Mt. Sinai Hospital
Baltimore, MD
"Prevention of Thromboembolism"
"Management of Ovarian Cancer"

- 1992** Visiting Professor - Department of OB/GYN
University of Massachusetts
Worcester, Massachusetts
- 1991** Visiting Professor
George Washington University School of Medicine
- Course Director - ACOG Course (120 series)
Annual Clinical Meeting
New Orleans, Louisiana
"Gynecologic Oncology for the Practicing Gynecologist"
- Course Director - ACOG Course
Vancouver, British Columbia, Canada
"Gynecologic Surgery"
- Visiting Professor
Florida Hospital Cancer Center
Orlando, Florida
- Paper Presentation
Poster Presentation
Society of Gynecologic Oncologists
Orlando, Florida
- Visiting Professor
Ohio State University School of Medicine
Columbus, Ohio
- Medical Oncology Board Review Course
George Washington University
Washington, DC
"Cervical, Vulvar and Vaginal Cancer"
"Gestational Trophoblastic Disease"
- 1990** Society of Gynecologic Oncologists
Breakfast Seminar
"Diagnosis and Prevention of Postoperative Venous Thrombosis"
- Course Director - ACOG Course (120 Series)
Annual Clinical Meeting
San Francisco, California
"Update in Clinical Gynecologic Oncology"
- Seminar, ACOG Clinical Meeting
"Prevention of Postoperative Venous Thrombosis"
- 1989** Tumor Conference, Moore Regional Hospital
Pinehurst, North Carolina
- Course Director - ACOG Course (120 Series) Annual Clinical Meeting, Atlanta, Georgia
"Update in Clinical Gynecologic Oncology"
- Seminar, ACOG Clinical Meeting
"Management of Early Ovarian Cancer"

Luncheon Conference, ACOG Annual Meeting
"Reproductive Outcome Following Cancer Treatment"

Medical Oncology Board Review Course, George Washington University, Washington, DC
"Cervical Cancer"

1988 Matt Weiss Symposium
St. Louis, Missouri

ACOG Annual Clinical Meeting
Poster Session Presentation
Review of Clinical Research Paper
Review of Surgical Film
Clinical Seminar Presentation

ACOG Course
Juneau, Alaska
"Gynecologic Surgery"

1987 Update in Obstetrics and Gynecology
Williamsburg, Virginia

North Carolina Obstetrical and Gynecological
Society Meeting, Southern Pines, North Carolina

Visiting Professor, University of Minnesota School of Medicine, Minneapolis, Minnesota

ACOG Annual Clinical Meeting
Clinical Paper Presentation
Clinical Seminar Presentation

Southern Obstetrics and Gynecology Seminar
Asheville, North Carolina

Satellite Teleconference
Chicago, Illinois
"Selected aspects of the care of the menopausal woman"

Chicago Medical Schools' Review Course
Chicago, Illinois
"Endometrial Carcinoma"

Smokey Mountain Obstetric and Gynecologic Seminar, East Tennessee State University
Johnson City, Tennessee

Grants

Active Grants:					
None at this time					
Completed Grants:					

Project Period	Agency	Title	Amount	Role	% of Effort
9/27/05-3/10/10	NIH/NICHD	Women's Reproductive Health Research (WRHR) Career Development Center at UNC - HDD050113-02	\$370,367 Annual Direct Costs	Principal Investigator	
3/1/00-3/31/02	Pharmacia Upjohn Pharmaceuticals	Randomized Comparison of Low Molecular Weight Heparin vs. Oral Anticoagulant Therapy for Long Term Anticoagulation in cancer patients – 98-Frag-069	\$ 73,000	Principal Investigator	
1/1/99-6/15/00	Zeneca Pharmaceuticals, Inc	Phase II/III Trial of IV ZD9331 in patients with recurrent refractory ovarian cancer	\$ 18,320	Principal Investigator	
6/1/98-6/1/00	Pharmacia Upjohn Pharmaceuticals	Prospective Randomized Trial Comparing Pneumatic Compression stockings To Low Molecular Weight Heparin (dalteparin) in the prevention of postoperative venous Thrombosis	\$ 100,760	Principal Investigator	
06/01/95 - 05/31/2000	National Cancer Institute	Hyperthermia and Perfusion Effects in Cancer Therapy	\$10,930,969	Investigator	2%
03/15/98-03/14/00	Novartis Pharmaceuticals	PSC 833 with taxol and carboplatin vs. carboplatin alone in patients with stage III ovarian cancer	\$ 102,240	Principal Investigator	
8/1/97-7/31/99	NIH	Hyperthermia and Perfusion Effects in Cancer Therapy	\$ 1,832,501	Co-Investigator	
5/28/97-12/31/98	Smithkline Beecham Pharmaceuticals	Oral Topotecan Single Agent for 5 days in patients with ovarian cancer	\$ 81,600	Principal Investigator	
01/01/93-12/31/98	National Cancer Institute	Comprehensive Cancer Center Core Support Grant	\$ 4,442,597	Program Director	10%
06/01/94 -	National Cancer	Autologous Bone	\$641,613	Investigator	10%

03/31/97	Institute	Marrow Transplantation in Breast and Ovarian Cancer: Project IB			
03/15/96-05/30/96	Ethicon, Inc	An Open, Controlled, Rand, Multicenter, Evaluation of Dyed Monocryl (Poliglecaprone 25) Synthetic Absorbable Suture as Compared to Surgical Gut (Chromic) Absorbable Suture	\$ 4,000	Principal Investigator	
1987-1996	American Cancer Society	Clinical Oncology Fellowship	\$ 20,000 (Direct)	Principal Investigator	5%
10/01/92-09/30/94	Centocor, Inc.	CA125 Post-Market Evaluation	\$ 8,750	Principal Investigator	5%
12/15/93-09/21/94	Smith-Kline Beecham Pharmaceutical	Phase III Topotecan versus Taxol in Women with Advanced Ovarian Carcinoma	\$ 37,500	Principal Investigator	5%
12/15/93-08/14/94	Smith-Kline Beecham Pharmaceutical	II Topotecan, Given as Five Daily Doses Every 21 Days in Ovarian Cancer	\$ 37,500	Principal Investigator	10%
07/01/89 - 03/31/94	Gynecologic Oncology Group	Gynecologic Oncology Group, Duke University Medical Center	\$ Contingent on number of patients	Co-Principal Investigator	30%
01/01/91 – 09/01/93	Organon, Inc.	ORG 2766 as a Neuroprotector from Cisplatin Chemotherapy for Ovarian Cancer	\$97, 575	Principal Investigator	10%
02/01/91 - 01/31/92	Organon, Inc.	Decapeptyl Treatment of Advanced Ovarian Cancer (Phase II Trial)	\$100,098	Principal Investigator	10%
11/01/90-10/31/91	Cytogen, Inc.	111In-CYT-103 Oncoprobe Evaluation of Ovarian Cancer	\$ 124,000	Principal Investigator	10%
07/01/86-06/30/91	National Institutes of Health	Avoidable Mortality from Cancers in Black Populations	\$ 4,647,291	Co-Investigator	10%
06/01/87 - 05/31/89	Public Health Service	Improved Instrumentation for the Diagnosis of Venous Thrombosis	\$162,804 (Direct)	Co-Principal Investigator	10%
05/01/88 -	National Cancer	Gynecologic	\$97,073	Co-Principal	10%

04/30/89	Institute	Oncology Group, Duke University Medical Center	(Direct)	Investigator	
01/01/88 - 12/30/88	Centocor, Inc.	Evaluation of the Safety and Preliminary Diagnostic Accuracy of IV Administered Indium-111-labeled OC-125 Monoclonal Antibody in Patients with Carcinoma of the Ovary	\$ 20,000 (Direct)	Co-Principal Investigator	5%
01/01/88 - 12/30/88	Centocor, Inc.	Evaluation of the Safety and Preliminary Diagnostic Accuracy of IV Administered Indium-111-labeled OV-TL3 Monoclonal Antibody in Patients with Carcinoma of the Ovary	\$ 40,000 (Direct)	Co-Principal Investigator	5%
05/01/85- 04/30/87	National Cancer Insitute	Illinois Cancer Council - Gynecologic Oncology Group	\$ 21,000 (Direct)	Co-Principal Investigator	10%
07/01/81- 06/30/84	American Cancer Society	Junior Faculty Clinical Fellowship	\$ 35,000	Principal Investigator	30%
01/01/83- 12/31/83	Trent Foundation	In-vitro chemotherapy sensitivity testing of ovarian carcinoma	\$ 1,000	Principal Investigator	5%

PROFESSIONAL SERVICE

To discipline:

A. National/International

- 2018** President, Council of University Chairs of ObGyn (CUCOG)
- 2016** President Elect: Council of University Chairs of ObGyn (CUCOG)
- 2016 Vice President: Bayard Carter Society (Duke University ObGyn Alumni)
- 2016 Member, ACOG Grievance Committee
- 2016 Member, American College of Surgeons, Commission on Cancer
- 2016 American College of Obstetricians and Gynecologists)
- 2016
- 2015** Secretary-Treasurer: Council of University Chairs of ObGyn (CUCOG)
- 2015 American College of Surgeons Board of Governors. ACOG Representative (alternate)

2014

2014 Chair, External Site Visit Committee, Department of Obstetrics and Gynecology, Penn State
2014 University College of Medicine, Department of Obstetrics and Gynecology Member,
CUCOG Executive Board

2011

2011 Member, American College of Surgeons Advisory Committee (ObGyn)
2011 Member, CUCOG Executive Committee
2011 Chair, ACOG Committee on Gynecologic Practice
Chair, SGO Nominating Committee

2010-2013

2010-2013 Immediate Past President, SGO
2010-2013 Member, ACOG Executive Board (Representing the Society of Gynecologic Oncology)
2011-2013 Chair, Committee on Gynecologic Practice, ACOG
2007 -2010 Member, Education/Research Committee, Society of Pelvic Surgeons
1988- 2005 Board Examiner: Obstetrics and Gynecology , ABOG
2010-2011 Vice-Chair, Committee on Gynecologic Practice, ACOG
2010 President, Society of Gynecologic Oncologists
2009-2010 Editorial Board, Precis, Gynecology, ACOG
Program Chair, Society of Pelvic Surgeons

2008

2008-2010 Committee on Gynecologic Practice, ACOG
2008 President Elect II, Society of Gynecologic Oncologists
2008 Chair, Membership Committee. Society of Pelvic Surgeons
2007-2008 Vice President, Society of Gynecologic Oncologists

2007

2007 Editorial Board: Precis, Oncology, ACOG
2007 SGO Executive Council, Society of Gynecologic Oncologists
2007 Chair, Task Force to select Editor and Chief, Gynecologic Oncology, Society of
Gynecologic Oncologists
2007 Co-Chair, Strategic Planning Committee, Society of Gynecologic Oncologists
2007 Member, By-laws Committee, Society of Gynecologic Oncologists

2005

2005 NC Breast and Cervical Cancer Control Program's (BCCCP) Medical Advisory
Committee, North Carolina Department of Environment, Health, and Natural Resources
2005 Member, Clinical Cancer Committee, Moses Cone Health System
2005 Director, Gynecologic Oncology Program, Moses Cone Health System
2005 Member, Cancer Center Executive Committee, Moses Cone Health System
1998-2005 Member, Executive Committee Cancer Center Clinical Service Unit, Duke University
1998-2005 Co-Medical Director, Surgical Oncology Clinic, Duke University
1992-2005 Member, Operating Room Committee, Duke University
1991-2005 Principal Investigator, Duke University, Gynecologic Oncology Group
1987-2005 Director of Gynecologic Oncology Fellowship Program (Duke Univ), ABOG
1987-2005 Director, Gynecologic Oncology Program, Duke Comprehensive Cancer Center, Duke
University
1987-2005 Member, Steering Committee Strategic Planning Task Force, Duke Comprehensive
Cancer Center, Duke University
1987-2005 Member, Executive Committee, Duke Comprehensive Cancer Center, Duke University

2003

2003 Nominating Committee, Society of Gynecologic Oncologists
2003 President and Program Chairman, Mid Atlantic Gynecologic Oncology Society

2002

2002 President-Elect, Mid Atlantic Gynecologic Oncology Society
2002 Member, Membership Committee, Society of Pelvic Surgeons
2002 Member, Oncology Strategic Planning Council, Duke University

2001

2001 Editorial Board: Precis, Oncology, ACOG
2001 Board Examiner: Gynecologic Oncology, ABOG

2000

2000 Member, Nominating Committee (AGOS Foundation)
2000 Program Chairman (Annual Meeting), Mid Atlantic Gynecologic Oncology Society
1994-2000 Member, Education Committee, Society of Gynecologic Oncologists

1999

1996-1999 Member, Fellowship Committee, AGOS

1998

1994-1998 Council Member, Society of Gynecologic Oncologists
1990-1998 Ovarian Cancer Committee, Gynecologic Oncology Group

1997

1993-1997 Editorial Board Member, Duke Cancer Report, Duke University
1993-1997 Committee on Gynecologic Practice, ACOG
1993-1997 Chairman, Committee on Gynecologic Oncology Practice, ACOG
1993-1997 ACOG Liaison Representative to the Society of Gynecologic Oncologists
1994-1997 Member, Committee on Clinical Practice, Society of Gynecologic Oncologists

1995

1994-1995 Chairman, 1995 Program Committee, Society of Gynecologic Oncologists

1994

1993-1994 Ad hoc Council Member, Society of Gynecologic Oncologists
1993-1994 Ad hoc Committee on Clinical Practice Policy Development Society of Gynecologic
Oncologists
1994 Society of Pelvic Surgeons

1993

1991-1993 Chairman, Gynecology Committee, North Carolina OB/GYN Society
1991-1993 Member, Professional Activities Committee, North Carolina OB/GYN Society
1993 Medical Director, Duke North Hospital, 5900 Unit, Duke University
1993 Fellow, American Gynecological and Obstetrical Society
1993 Member, Ad hoc Committee to Define Criteria for Tenure in Clinical Medicine , Duke
University
1993 Department of Surgery Chairman Search Committee, Duke University

1992

1990-1992 Member, Task Force on Cervical Cancer, Chairman, Subcommittee on Impact of
Appropriate Follow-up Care, North Carolina Department of Environment, Health, and
Natural Resources

1991

1987-1991 Co-Principal Investigator, Duke University Grant, Gynecologic Oncology Group
1987-1991 Committee on Technical Bulletins, ACOG
1991 Board Examiner: Gynecologic Oncology, ABOG
1991 Member, Director of Surgical Pathology Search Committee, Duke University

1990

- 1990 Member, Department of Pathology Chairman Search Committee, Duke University
- 1982-1990 Gynecologic Management Committee, Gynecologic Oncology Group

1989

- 1989 Fellow, American College of Surgeons

1988

- 1988 Mid-Atlantic Gynecologic Oncology Society
- 1988 Southern Obstetrical and Gynecological Seminar
- 1988 International Gynecologic Cancer Society
- 1988 Mid-Atlantic Gynecologic Oncology Society
- 1988 Southern Obstetrical and Gynecological Seminar

1987

- 1985-1987 Chicago Medical Society
- 1985-1987 Illinois Cancer Council
- 1985-1987 Illinois State Medical Society
- 1985-1987 Chicago Association of Gynecologic Oncologists
- 1987 North Carolina Medical Society
- 1987 North Carolina Obstetrical and Gynecological Society
- 1987 American Society of Clinical Oncologists

1986

- 1986 Chicago Gynecological Society

1985

- 1982-1985 Co-Principal Investigator, Duke University Grant, Gynecologic Oncology Group
- 1985 Central Association of Obstetricians and Gynecologists
- 1985 Central Association of Obstetricians and Gynecologists
- 1985 American Medical Association

1982

- 1982 Gynecologic Oncology Group
- 1982 Society of Gynecologic Oncologists
- 1982 Fellow, American College of Obstetricians and Gynecologists

1979

- 1979 Piedmont Obstetrical and Gynecological Society
- 1979 Bayard Carter Society of Obstetricians and Gynecologists
- 1979 Junior Fellow Section Chairman, ACOG

1978

- 1978 Junior Fellow Section Co-Chairman, ACOG

1977

- 1977 Junior Fellow Section Program Chairman, ACOG

B. Within UNC-Chapel Hill

- 2018-2021 Member, School of Medicine Promotions and Tenure Committee
- 2013-present Member, UNC Hospitals Committee of Perioperative Leaders
- 2011-present Member, Physicians and Associates Executive Committee
 - Member, P&A Finance and Compensation Committee
 - Member, P&A Committee on Payer Relations

2009-present Member, Strategic Planning Committee: Hillsboro Hospital

2009-present Member, Strategic Planning Committee UNC HCS
2008-present Member, Dean's Advisory Committee on Part-Time Tenure Track Positions
2008-present Member Geographic Strategic Planning Committee
2008-present Member UNC Strategic Planning Committee: Outpatient Surgery
2008-present Member UNC Strategic Planning Committee: Oncology
2007-present Member, Sheps Center Advisory Board
2007-present Member, Center for Women's Health Research Advisory Board
2007-present Team Leader (Attending Physicians' Experience) UNC Hospital Commitment to Caring
2006-present Medical Director, NC Women's Hospital Ambulatory Services
2005-present Dean's Advisory Committee
2005-present UNC Hospital Executive Committee
2005-present Physician and Chief, North Carolina Women's Hospital
2005-present Member, Physician and Associates Board
2005-present Member, UNC Lineberger Cancer Center
2006, 2007 Chair, Data Safety Monitoring Board: An International Multi-Center Phase III Study of
Chemoradiotherapy versus chemoradiotherapy plus hyperthermia for locally advanced
cervical

Editorial Board Member

1994-2004 Postgraduate Obstetrics and Gynecology
2003 Précis, Oncology, Second Edition
1995-2001 Associate Editor, Journal of Gynecologic Techniques
1994-2000 Gynecologic Oncology

Journal Reviewer

Obstetrics and Gynecology
New England Journal of Medicine
American Journal of Obstetrics and Gynecology
Journal of the American Medical Association (JAMA)
Annals of Internal Medicine
Pharmacotherapy
Fertility and Sterility
Gynecologic Oncology
Cancer
International Journal of Gynecology and Obstetrics
Journal of Pelvic Surgery

Exhibit B

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- “Deposition & Exhibits of Julie Pier, MDL No. 2738.” In re: Talcum Power Prod. Liab. Litig., September 12, 2018.
- “Deposition of Alice M. Blount, Ph.D., Circuit Court of the City of St. Louis State of Missouri, Case No.: 1522-CC10417-01,” April 13, 2018.
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Exhibit C

DANIEL CLARKE-PEARSON, MD PRIOR TESTIMONY

Rappaport v. Raleigh Ob/Gyn Centre, P.A., et al., No. 14-CVS-1438. Superior Court of North Carolina, Wake County.

Exhibit 13

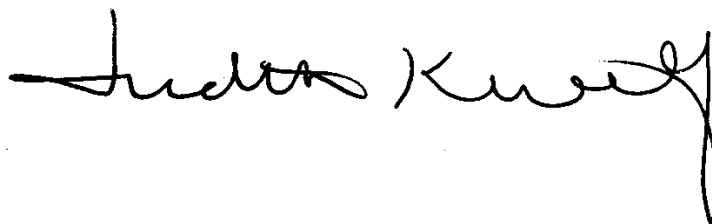
**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
JUDITH WOLF, MD**

A handwritten signature in black ink, appearing to read "Judith Wolf", with a long, vertical flourish extending from the end of the name.

Date: November 16, 2018

Judith Wolf, MD

I. BIOGRAPHY AND QUALIFICATIONS

I am a board certified gynecologic oncologist, a physician specializing in the care of women with cancer with more than thirty years experience. I attended medical school at Northeast Ohio Universities College of Medicine and then moved to Texas where I completed residency at the University of Texas San Antonio and fellowship at MD Anderson Cancer Center where I remained on faculty for more than twenty years as Professor in the Department of Gynecologic Oncology. My area of expertise is ovarian cancer - diagnosis, research, treatment, and patient advocacy.

I have authored or co-authored over 100 peer-reviewed research articles and was the principal investigator or co-investigator for eleven research grants related to gynecologic cancers. Additionally, I have served as the principal investigator, co-principal investigator, or collaborator on 84 protocols, and have presented at more than 50 conferences, as well as at numerous scientific exhibitions and seminars. The majority of these have dealt with some aspect of ovarian cancer.

My research began when I was a fellow in gynecologic oncology. In addition to two years of clinical training, I spent two years working in the lab and getting my Masters degree in Biomedical Science from The University of Texas School of Biomedical Sciences in Houston. My research as a graduate student was in investigating targets for therapy in ovarian cancer. One of these led to a phase I Clinical trial for women with ovarian cancer using a targeted therapy. This trial was part of a larger NCI grant. After completing training, I maintained a research lab for over ten years, investigating gene therapy for the treatment of both ovarian and cervical cancer. My laboratory research in ovarian cancer led to a Clinical trial of gene therapy for women with ovarian cancer. Being able to see the long road it takes to bring new therapies from the lab to clinic fostered my continued interest in clinical trials, and led me to become involved in both investigator initiated and NCI cooperative group clinical trials - Phase II and III trials of new therapies for ovarian cancer.

Throughout my tenure as a Professor at MD Anderson Cancer Center, I was recruited to join the biomedical industry. It wasn't until in 2014, when Vermillion at Diagnostic Company recruited me as a Chief Medical Officer that I felt compelled to make a change in my career path. By this point in time, I had cared for hundreds of women with ovarian cancer, and saw the devastation this disease causes, with little improvement in the overall prognosis in more than twenty years. Working with a diagnostic company, focused on the early detection of ovarian cancer, seemed to me to be another way I could work to make a difference. While at Vermillion, I co-authored several publications, helped the company gain FDA clearance for their second generation multiprotein biomarker assay for ovarian cancer detection and was integral in the company obtaining a \$7.5 million dollar grant from the State of Texas for ovarian cancer detection.

After two years at Vermillion, I was recruited by another small start-up diagnostic company, ProvistaDx, again in a Chief Medical Officer role. ProvistaDx was using similar multi-protein assays (like Vermillion) but combining them with antibodies to try to detect both breast and

ovarian cancer early. While at ProvistaDx, we published several articles in the breast cancer detection area and their first publication using this combined technology for ovarian cancer detection.

Working in these diagnostic companies exposed me to some of the intricacies of working in the biomedical industry and research from a view- from that as a public ally traded company (Vemillion) and a small private start-up (ProvistaDx). Additionally, I learned much about the regulation of the industry.

In mid-2018 I left my company position to have more time to focus on my volunteer and advocacy work for women's health- with a large focus on ovarian cancer.

In the mid 1990s, I became involved with raising awareness and educating women about ovarian cancer through my work with the National Ovarian Cancer Coalition. Initially, I was a medical board member and am currently a governing board member. Our mission is to raise awareness and educate women and their families about ovarian cancer. Additionally, I combined my love of running and passion for ovarian cancer to organize a charity 5K walk/run to raise awareness and research money for the Blanton/ Davis Ovarian Cancer Research Program at MD Anderson Cancer Center. This race has been going on now for more than twenty years and has raised more than \$5 million dollars for ovarian cancer research.

In 2014, I became a member of the board of the Society for Women's Health Research which is a National nonprofit dedicated to promoting research on biological differences in disease and improving women's health. Additionally, I began working with Health Volunteers Overseas. I have volunteered in Vietnam, Honduras and Haiti working with physicians in these countries to train them to be better able to care for women with gynecologic cancers. Working with HVO, for the past year and a half, I am heading a project training young surgeons in Nepal to care for women with ovarian, cervical and uterine cancers. To continue my mission of improving women's health here in the US, I am working part time in Indianapolis, IN as a Gynecologic Oncologist. My curriculum vitae is attached as Exhibit A.

II. METHODOLOGY

I was asked to make a determination as to whether the genital use of talcum powder can cause ovarian cancer. I approached this issue in a similar way and with the same rigor that I would use in my professional practice, both clinically and in research. This is an exercise I have used regularly throughout my thirty plus year career. I reviewed extensive medical and scientific literature (including epidemiological, animal, mechanistic studies, and reviews on all relevant topics). I also researched publicly available information related to talcum powder products, their safety, and their association with ovarian cancer. Many of these sources were obtained through articles and references from my personal library of journals, textbooks, as well as PubMed searches on relevant topics. Additional relevant literature, documents, and testimony were provided by the attorneys working on this case. I also requested additional information on various relevant issues when appropriate.

In doing this research, I applied the same standards that I use in clinical medicine to consider the reliability and validity of the medical and scientific literature, assessing the evidence according to the strengths and weaknesses of the study under review. I considered an extensive body of relevant literature, without regard to the nature of the specific findings. I based the opinions provided in this report using a weight of the evidence methodology in the context of Bradford Hill concepts.

III. OVERVIEW OF OVARIAN CANCER

Ovarian cancer is a group of malignancies that are believed to begin in ovarian or fallopian tube tissue. There are three groups of cancers based on the cell type from which they arise - germ cell, stromal, and epithelial cancers. Epithelial cancers (EOC) account for the vast majority of ovarian cancers (greater than 90%) and are further subdivided based on the microscopic characteristics of the cells. These subtypes include serous, endometrioid, clear cell, mucinous, undifferentiated or mixed. Of these, serous is by far the most common and accounts for 70% of EOC. Epithelial ovarian cancers are those that are associated with talcum powder products.

Epithelial carcinoma of the ovary, fallopian tube, and peritoneum are usually considered as a single entity due to their common clinical behavior, risk factors, and pathogenesis. Over the past decade, research has found that many serous carcinomas of the ovary may begin in the cells that line the distal portion of the fallopian tube. These cells then leak, drip, or “escape” from the tube and the ovary (which is next to the tube) or the peritoneum (the layer that lines the inside of the abdomen and pelvis). (Levanon 2008, Chen et al. 2017; Singh et al. 2016; Soong et al. 2018) Cancers that clinically appear to arise from the fallopian tube, ovary or peritoneum have the same microscopic appearance, pattern of spread (throughout the pelvis and abdomen), and response to treatment. This information is consistent with the role of talcum powder in cancer development.

Ovarian cancer is a relatively rare cancer. The American Cancer Society estimates in 2018 22,240 new cases of ovarian cancer compared to 268,670 new cases of breast cancer.¹ There is no screening for ovarian cancer and symptoms are vague. This presentation leads to late diagnosis for more than 75% of patients. Because of these factors and the often aggressive nature of the tumors, ovarian cancer is the most deadly gynecologic malignancy in the U.S. Seventy to seventy-five percent of women with advanced stage EOC die from their disease, usually from bowel obstruction, following years of chemotherapy treatment.² (Chen, L-M, et al 2018).

The National Cancer Institute defines a risk factor as something that increases the chances of developing a disease. Associations can occur that are not actually linked with a disease. A causative risk factor is one that increases the chances of developing a disease by means of a

¹ <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>

² *Id.*

known or predictable mechanism. In other words, it is more than a mere association. (Vineis 2017).

The most significant risk factor associated with ovarian cancer are inherited susceptibility genes, primarily BRCA1, BRCA2, and the mismatch repair genes (associated with Lynch syndrome). A woman with BRCA1 gene mutation has a 39-46% lifetime risk of developing ovarian cancer; a woman with BRCA2 gene mutation has an 11-27% lifetime risk of developing ovarian cancer. (Ring et al. 2017). It is estimated that these hereditary gene mutations account for 10-15% of all ovarian cancer and 75% of all hereditary ovarian cancers. (Lancaster et al. 2015). It is important to distinguish these inherited gene mutations from induced mutations caused by inflammation or environmental insults.

In addition to talc and asbestos exposure, other risk factors that have been linked to EOC include increasing age, nulliparity, infertility, endometriosis, obesity, polycystic ovarian syndrome, use of an intrauterine device, history of pelvic inflammatory disease, and cigarette smoking (for mucinous carcinoma). Protective factors (associated with a decreased risk of EOC) include previous pregnancy, history of breastfeeding, oral contraceptives, and tubal ligation. (Hunn and Rodriguez 2012; Mallen, Townsend, and Tworoger 2018; Park et al. 2018; Folkins et al. 2018). It is important to note that risk factors can interact with each other or act independently. They can act in a cumulative, additive, and/or synergistic fashion. (Wu et al. 2018; Vitonis et al. 2011).

Talcum powder dusting is often referred to as a “lifestyle factor”. There are no medical benefits; any risk, particularly a risk of something as devastating and deadly as ovarian cancer, is unacceptable. (Folkins et al. 2018) Because of this, I advise all my patients not to use talcum powder products or to stop using them if they are already doing so.

Most women with EOC present with pelvic or abdominal pain, bloating, and/or gastrointestinal symptoms. Diagnosis is based upon pathologic evaluation of tissue. Knowledge and evaluation of the pathology of ovarian cancer is part of every gynecologic oncologist’s training and experience. Staging is surgical. In a patient with advanced stage ovarian cancer (stage 3 and 4), the cancer is spread throughout the abdomen and pelvis with typically thousands of tumor nodules covering the surface of all internal organs, along with several liters of fluid containing cancer cells (ascites).

Treatment for ovarian cancer is a combination of surgery and chemotherapy. Most women with advanced disease obtain 1-2 years of remission after treatment, and then their cancer recurs. Once ovarian cancer recurs, it is not curable and most patients spend the remainder of their life on chemotherapy in an attempt to extend their life spans and minimize their often severe symptoms.

IV. HISTORICAL BACKGROUND OF TALC

Johnson and Johnson’s baby powder was introduced to consumers in 1894. (Gurowitz 2007).

In the late 1940s and early 1950s, there were numerous articles (including at least one from Johnson and Johnson's own lab) describing the inflammatory properties of talc when introduced into the peritoneal cavity experimentally or through surgical gloves and the relative safety of starch products in the same setting. (Eberl and George 1948; Graham and Jenkins 1952). In 1953, Johnson and Johnson submitted a patent application for a "non-irritating" starch-based dusting powder due to the severe postoperative complications and strong inflammatory reaction frequently caused by talc. (Caldwell et al. 1953). In 1967, the association between asbestos and ovarian cancer was reported (J. Graham and Graham 1967).

Henderson first identified talc particles deep in ovarian tissue in 1971. (Henderson et al. 1971). Dr. Woodruff and colleagues at Johns Hopkins began raising awareness regarding environmental toxins like talc as etiologic factors in the pathogenesis of ovarian cancer in the early 1970s. (Parmley and Woodruff 1974).

In 1979, Longo and Young cautioned the cosmetic industry regarding the dangers of talc in *The Lancet*: "Epidemiological, experimental, and clinical data seem to link asbestos and talc with ovarian cancer. Direct passage of talc or asbestos-contaminated talc through the female reproductive tract to the ovarian surface may play an aetiological role. Further systematic evaluation of talc and asbestos as ovarian carcinogens is needed. . . . What is disturbing is that a consultant to the cosmetic industry feels that further research on the biological effects of talc 'merits little priority'". (D. L. Longo and Young 1979). The first epidemiologic study on the association between talc and ovarian cancer was published in 1982. (Cramer et al. 1982).

Between 1992 and 1995, concerns were raised in the medical literature regarding risks, including ovarian cancer, of talc on condoms. (e.g., Kang, Griffin, and Ellis 1992; Kasper and Chandler 1995). In 1995, the condom industry voluntarily agreed to stop dusting condoms with talc due to ovarian cancer concerns. ("PCPC_MDL00062175" 1999; McCullough 1996). Recommendations regarding the use of talcum powder on diaphragms were also discontinued in the late 1990s. In 1998, Janssen, a subsidiary of Johnson & Johnson, changed the warning on its All-Flex Diaphragm to state "Powders should not be used with the diaphragm."³

V. EPIDEMIOLOGY

Since the early 1980's, there have been numerous epidemiological studies evaluating the risk of ovarian cancer with talcum powder usage. To the present time, there are over 25 case-control studies, three prospective cohort studies, one pooled analysis, and seven meta-analyses. I assessed all of these studies.

A case-control study is designed to help determine if an exposure is associated with an outcome, in this case ovarian cancer. First, researchers identify women with and without ovarian cancer - cases and controls. Then they look back in time to learn which subjects in each group had talcum

³ Janssen sold the Ortho diaphragms beginning in the 1960s. The 1962 instructions stated, "Dust diaphragm when dry with talcum powder and return it to the original container." (JANSSEN-000001-19) 1962).

powder exposure(s), comparing the frequency of the exposure in the case group to the control group.

A case-control study is always retrospective because it starts with an outcome then traces it back to investigate exposures. Advantages of case-control studies are that they are comparatively efficient, less expensive, and easier to perform. Potential weaknesses include selection bias, (because they are not randomized) and recall bias. Case-control studies are particularly appropriate for uncommon diseases, like ovarian cancer, in which a very large cohort would be required to accumulate enough cases for analysis. (Narod 2016).

A cohort study follows a group of people with defined characteristics, such as talcum powder exposure, and who are followed to determine incidence of an outcome, in this case development of ovarian cancer. Cohort studies can be retrospective or prospective. They can calculate rates of disease in exposed and unexposed individuals for multiple outcomes over time. Potential disadvantages of cohort studies include the requirement of large number of subjects for rare exposures and outcomes and long duration of follow up for certain conditions.⁴ These disadvantages apply to the study of talc and ovarian cancer. Narod estimated that, for a cohort study to be properly powered to accurately predict the risk associated with talc use and ovarian cancer, as many as 200,000 women may be necessary. (Narod 2016).

A meta-analysis combines the results from previous studies to derive conclusions from a larger set of data. Outcomes from a meta-analysis may include a more precise estimate of the effect of treatment or exposure (talcum powder) than any individual study contributing to the pooled analysis.⁵ A meta-analysis weights the strengths of the studies before combining the data, unlike a pooled study. A meta-analysis can be especially useful to review a complex, sometimes conflicting body of literature.

A randomized control trial, in which participants are divided by chance into separate groups to compare different interventions, is considered the gold standard in some research situations. However, it would be unethical and impractical to conduct a prospective randomized control clinical trial to compare the outcomes of women who did and did not use genital talcum powder because of its known carcinogenic potential.

For this project, I reviewed all epidemiological studies related to talcum powder and ovarian cancer, but concentrated on the cohort studies, the meta-analyses, and more recent high-quality case-control studies. I critically analyzed factors such as study design, journal quality, number of subjects, length of follow-up, and potential biases.

Case-Control Studies

There are numerous case-control studies. Overall, the case-control studies are consistent showing a 30-50% increase in risk of ovarian cancer with talcum powder use. I found the most

⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2998589/>

⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049418/>

recent ones to be the most useful, based on their size and quality of design. Several are summarized below:

A study by Wu published in 2015, evaluated 1701 women with EOC in California. The conclusion of this study found that talc significantly increased the risk of ovarian cancer – 40% in whites, 20% in Hispanics, and 56% (not statistically significant) in African Americans. The number of African Americans with ovarian cancer was only 128 and may account for the non-significant increase. (Wu et al. 2015).

Cramer published a recent case-control study of nearly 4,000 women in Massachusetts and New Hampshire with ovarian cancer and found that genital use of talcum powder, either alone or in combination with body use, was associated with a statistically significant elevated epithelial ovarian cancer risk (OR 1.33). Risk increased with frequency and duration of use. Talcum powder use increased risk for serous and endometrioid tumors with the dose response most apparent for invasive serous cancer. (Cramer et al. 2016).

A multi-center study sponsored by National Cancer Institute of epithelial ovarian cancer in African-American women, a group with a high prevalence of talcum powder use, determined that regular genital powder use was associated with an increased risk of epithelial ovarian cancer (OR 1.44). A dose-response relationship was found for duration of use and number of lifetime applications ($P < 0.05$). Additionally, talcum powder use was common (62.8% of cases and 52.9% of controls). (Schildkraut et al. 2016).

Cohort Studies

The Nurses' Health Study (NHS) is a prospective study of 121,700 nurses who were aged 30-55 years at enrollment in 1976 and followed through 1996 at the time of the publication. In the NHS, talcum powder use was ascertained once in 1982, the same year as the first case-control study showing an association of talc use with ovarian cancer. (Cramer et al. 1982). The follow up period for this study was 12.9 years. The study concluded there was no overall association with talc "ever use" and epithelial ovarian cancer. However, there was a statistically significant increase risk of invasive serous ovarian cancer (40%) that was higher with more frequent talcum powder use. The short period of follow up may not account for all ovarian cancer cases due to latency considerations between talcum powder usage and the development of ovarian cancer. (Gertig et al. 2000). A second report of the Nurses' Health Study in 2010 did not find a statistically significant increased risk with talcum powder usage and either epithelial cancer as a whole or serous subtype. (Gates et al. 2010).

The Women's Health Initiative (WHI) enrolled 93,676 women from 1993-1998. Women were eligible if they were aged 50 to 79 (mean 63.3 years) at enrollment and postmenopausal. Mean follow-up was 12.2 years. Use of powder on the genitals was associated with 12% increased risk of ovarian cancer, though this was not statistically significant. Limitations of this study include lack of information regarding oophorectomy and recall bias regarding history of talc "ever use". Additionally, the short follow-up may not account for all cases of ovarian cancer. Information regarding the frequency or duration of powder usage was not obtained. (Houghton et al. 2014).

The Sister Study (2003-2009) followed 50,884 women in the US and Puerto Rico who had a sister diagnosed with breast cancer. At enrollment, participants were asked about douching and talcum powder use in the previous twelve months. During follow-up (median 6.6 years) 154 women reported a diagnosis of ovarian cancer but only seventeen of those reported talc use. The authors determined that there was little association between baseline talcum powder use and subsequent ovarian cancer. Douching at baseline, more common in talc users, was associated with increased risk. All ovarian cancers were grouped together. Limitations of this study include: 1) talc use was only obtained at baseline and was uncommon (analysis was based on only 17 cases), 2) no histologic information was obtained, so it is impossible to analyze relationship to serous subtype, 3) no risk elevation has ever been reported with dusting of diaphragm, cervical cap, or sanitary napkins, and 4) the short follow-up fails to account for the latency period. (Gonzalez et al. 2016).

All of the cohort studies are limited by lack of power, failure to make the appropriate queries, selection bias, and short follow-up.

Meta-Analyses

A recent and comprehensive meta-analysis by Penninkilampi and Eslick, published in 2018, included 24 case-control (13,421 cases) and three cohort studies (890 cases). The authors found that “any” perineal talc use was associated with an increased risk of ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). More than 3600 lifetime applications (OR = 1.42; 95% CI 1.25, 1.39) were slightly more associated with ovarian cancer than <3600 (OR = 1.32; 95% CI = 1.15, 1.50). An association with “ever use” of talc was found in case-control studies (OR = 1.35; 95% CI = 1.27, 1.42), but not cohort studies (OR 1.06; 95% CI = 0.90, 1.25). However, cohort studies did find an association between talc use and invasive serous ovarian cancer (OR = 1.25; 95% CI = 1.01, 1.55).

The authors stated that case-control studies are preferred in this situation because statistical power is easier to obtain with the larger number of ovarian cancer cases and controls and the lengthy follow-up necessary for a prospective study is not required. I agree. The authors determined that perineal talc use is associated with a 24%–39% increased risk of ovarian cancer that is suggestive of a causal association. (Penninkilampi and Eslick 2017).

Summary of Epidemiological Evidence

When looking at epidemiological studies in their totality, the data demonstrates a consistent, replicated, and statistically significant increased risk of developing epithelial ovarian cancer with perineal talcum powder use. Invasive serous carcinoma is the most commonly associated histologic subtype. The risk elevation is 20-60%. This risk is stable among case-control studies, one cohort study, and all meta-analyses/pooled analyses over several decades. Recall and confounding bias in case-control studies appear to have minimal impact. (Penninkilampi and Eslick 2018; Langseth et al. 2008). There appears to be no significant publication bias. (Berge et al. 2017; Penninkilampi and Eslick 2018). Meta-analysis is the most reliable and scientifically valid epidemiological methodology in this setting - the evaluation of the association of talcum powder usage with ovarian cancer risk

VI. ASBESTOS AND OTHER CONSTITUENTS OF TALCUM POWDER

Asbestos is one of the most potent carcinogens known. All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) are carcinogenic to humans. (IARC 2012) The conclusions reached by International Agency for Research on Cancer (IARC) about asbestos and its carcinogenic risks apply to these six types of asbestos wherever they are found, and *includes talc containing asbestiform fibres* (fibrous talc). (IARC 2012). Asbestos was first linked to pulmonary mesothelioma in 1935 (Gloyne 1935) and has been known to be an etiologic factor for ovarian cancer since 1965. (J. Graham and Graham 1967).

According to IARC, asbestos causes mesothelioma of the lung, larynx, *and ovary*. Based on multiple positive cohort mortality studies of women with heavy occupational exposure to asbestos, IARC's Working Group determined there is a causal association between asbestos exposure and ovarian cancer. (IARC 2012).

The scientific literature, Johnson and Johnson testing results and documents, and testing results of Dr. William Longo and Dr. Mark Rigler have demonstrated that talcum powder products, including Johnson's Baby Powder and Shower to Shower, may contain asbestos. (Cralley et al. 1968; Rohl et al. 1976; Lockey 1981; Paoletti et al. 1984; Blount 1991; Werner 1982; "Deposition of Alice M. Blount, Ph.D., Circuit Court of the City of St. Louis State of Missouri, Case No.: 1522-CC10417-01" 2018; Exhibit 28, Deposition of John Hopkins, Ph.D., MDL No. 2378, 2018; Exhibit 47, Deposition of Julie Pier, MDL 2738, 2018).

The IARC 2012 Monograph on asbestos states, "consumer products (e.g., cosmetics, pharmaceuticals) are the primary source of exposure to talc for the general population. Inhalation and *dermal contact* (i.e., through perineal application of talcum powders) are the primary routes of exposure." (IARC 2012).

Asbestos exposure is known to cause ovarian cancer; its presence in Johnson and Johnson talcum powder products contributes to the carcinogenicity of the products through an established mechanism of inflammation, DNA damage, and genetic alterations. Asbestos fibers may directly induce DNA damage mediated by reactive oxygen species. Asbestos fibers have also been shown to physically interfere with the mitotic apparatus, which may result in aneuploidy or polyploidy, and specific chromosomal alterations characteristic of asbestos-related cancer. In addition, persistent inflammation and macrophage activation can secondarily generate additional reactive oxygen species and reactive nitrogen species that can indirectly induce genotoxicity in addition to activation of intracellular signaling pathways, resistance to apoptosis, stimulation of cell proliferation, induction of epigenetic alterations, and activation of oncogenes/inactivation of tumor suppressor genes. (IARC 2012; Kane et al. 1996; Mossman 2018; Shukla et al. 2009; M. C. Jaurand 1997, 1989; M. Jaurand 1991)

In addition to asbestos, talcum powder products have been shown to contain fibrous talc, nickel, and chromium. These are Group 1 carcinogens according to IARC. The inflammatory mechanism for carcinogenesis described by IARC is similar to that described for asbestos and talcum powder. These products also contain cobalt which is a Group 2b carcinogen according to

IARC (possibly carcinogenic), defined previously in this report.(W. E. Longo and Rigler 2018; Exhibit 47, Deposition of Julie Pier, MDL 2738, 2018)

I have also seen the list of “fragrance chemicals” added to Johnson’s Baby Powder and Shower to Shower products, as well as the expert report of Dr. Michael Crowley. Many of these chemicals are known to be irritants, toxins, and carcinogens. Some have been shown to be harmful to the reproductive organs and function. These chemicals would be expected to accompany the talcum powder as it migrates or is transported through the genital tract to the fallopian tubes and ovaries. At least some of these chemicals would also be expected to be absorbed through the vaginal mucosa. These chemicals likely contribute to the inflammatory properties, toxicity, and carcinogenicity of these talcum powder products.

The presence of these constituents provides support for the mechanism for the increased risk seen in the epidemiological studies.

VII. MIGRATION AND TRANSPORT OF TALC THROUGH THE GENITAL TRACT

In the adult female, the peritoneal cavity communicates with the outside via the fallopian tubes, uterus, and vagina. It is universally accepted in the gynecologic community that substances migrate and/or be transported in both directions. Evidence to support this includes, but is not limited to:

1. Sperm: Sperm move more quickly through the genital tract than would be predicted from innate motility, indicating a transport mechanism. In addition, dead sperm and inanimate sperm particles (lacking flagella) are efficiently transported upwards through the uterus and tubes. (Jones and Lopez 2006). This process involves directed uterine contractility that has been confirmed through research of intrauterine pressure measurements. (Kissler et al. 2004).
2. Carbon particles: Inert carbon particles were placed in the posterior vaginal fornix and observed in the fallopian tubes 28 and 34 minutes later (2 out of 3 patients tested). This research confirmed that sperm motility is not the chief factor in transport and that contractions of the uterus are likely involved in process of migration/transport of particles through the genital tract. (Egli and Newton 1961).
3. Retrograde menstruation: The transport of menstrual flow into the peritoneal cavity was first proposed by Sampson in 1927 and is now well-established as the mechanism for endometriosis initiation. The prevalence of retrograde menstruation has been described in 90% of investigated women. (Blumenkrantz et al. 1981; Halme et al. 1984).
4. Particulate radioactive material: Particulate radioactive material was placed in the posterior vaginal fornix. Twenty four hours later, radioactive material was present in the adnexa separate from the uterus in 2/3 of cases. The authors concluded that the transit of particles from the vagina to the peritoneal cavity and the ovaries “is probably the same

for many chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties . . . migration of certain chemical substances could play an important aetiological role in gynaecological diseases and especially in carcinoma of the ovary.” (Venter and Iturralde 1979).

5. “Uterine peristaltic pump”: Rapid and sustained sperm transport from the cervix to the fallopian tube is provided by uterine peristaltic contractions that can be visualized by vaginal sonography. (Kunz 1997; Zervomanoklakis et al. 2007).
6. Glove powder: Studies have demonstrated retrograde migration of starch after gynecological examination with powdered gloves. The authors concluded that: “Consequently, powder or any other potentially harmful substances that can migrate from the vagina should be avoided.” (Sjösten, Ellis, and Edelstam 2004).
7. Talc: Studies have documented the presence of talc particles in the adnexa, ovaries, and peritoneum. The authors of these studies have concluded that this occurs as a result of migration of talc particles from the vagina through the cervix, uterus, and fallopian tubes. (Henderson et al. 1971; D. W. Cramer 1999; Heller et al. 1996). Talc has also been noted in pelvic lymph nodes which could also occur through migration, absorption, or inhalation with transport through the lymphatic system. (Cramer et al. 2007).

The migration of particles, including talc, asbestos and other constituents of talcum powder products, from the vagina to the upper genital tract (tubes and ovaries) is a key element in the mechanism by which talcum powder products cause ovarian cancer. The evidence supporting this process is robust and universally accepted by the medical community.⁶ (FDA Citizens Petition response) I have considered the limited evidence to the contrary and find it non-persuasive.

In addition to perineal application resulting in migration and transport of particles through the genital tract, inhalation of these particles is another recognized route of exposure. (IARC 2012; W. E. Longo, Rigler, and Egeland 2017; Steiling et al. 2018; Daniel W. Cramer et al. 2007) With either of these routes, talcum powder components can also be directly absorbed into the lymphatic system and bloodstream.

VIII. INFLAMMATION AND MOLECULAR BASIS FOR CARCINOGENESIS OF TALCUM POWDER PRODUCTS

The link between inflammation and cancer has been recognized since the 1800s. Inflammation and oxidative stress increase the risk of cancer, including ovarian cancer. It has been known since the 1940’s that talc increases inflammation. (Balkwill and Mantovani 2001; Eberl and George 1948).

⁶ FDA states that the “potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable.

There is an increased risk of malignancy with many inflammatory processes, including infection, autoimmune diseases, hypoxia, and chemical and physical agents (including talc and asbestos).

1. Virchow noted inflammatory cells (leukocytes) in neoplastic tissue as early as 1863.
2. Both tumor cells and inflammatory cells produce cytokines and chemokines which can contribute to cancer growth and spread.
3. Cytokines from inflammation/oxidative stress can influence multiple steps of the neoplastic process: survival, growth, mutation, proliferation, differentiation, and movement of cells. (Balkwill and Mantovani 2001; Reuter et al. 2010; Crusz and Balkwill 2015; Kiraly et al. 2015). Below are examples of inflammatory cytokines and their influence on cancer:
 - a. Tumor necrosing factor (TNF) can induce reactive oxygen (nitric oxygen (NO)) which can cause DNA damage. DNA damage can also occur by inhibiting cytochrome p450.
 - b. Migration inhibitory factor (MIF) can inhibit the activity of p53 which is a tumor suppressor.
 - c. IL-6, IL-1, IL-8 are all known to stimulate tumor cell proliferation and survival.
 - d. Multiple inflammatory cytokines (TNF, IL-1, IL-6, TGF beta 1) can stimulate angiogenesis.
 - e. TNF and IL-1 stimulate adhesion to promote invasion and metastasis of cancer cells.
4. Inflammation/oxidative stress affects all phases of cancer development and growth and is implicated in pathogenesis of ovarian cancer. This leads to decreased apoptosis and increased anaerobic metabolism. Anaerobic metabolism leads to an acidic state which facilitates cancer growth. (G. Saed 2017; G. M. Saed et al. 2010; Jiang et al. 2011; Shan and Liu 2009; Freedman et al. 2004)
5. Talcum powder causes inflammation/oxidative stress both *in vitro* and *in vivo* (in both animal and human tissues). (Eberl and George 1948; Graham and Jenkins 1952; Hamilton et al. 1984; Buz'Zard and Lau 2007; Shukla et al. 2009; G. Saed 2017; G. M. Saed et al. 2010; G. Saed 2017; Fletcher, Nicole, Memaj, Ira, and Saed, Ghassan 2018; N. Fletcher and Saed 2018, 2018; N. M. Fletcher et al. 2017, 2011; "NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3Fl Mice (Inhalation Studies)" 1993; Keskin et al. 2009).
6. In a recently reported abstract, Harper and Saed describes induction gene point mutations after talcum powder exposure, corresponding to known specific single nucleotide polymorphisms (SNPs) in normal and ovarian cancer cells. These SNPs alter the activities of key oxidant enzymes and enhance the pro-oxidant state. (Harper and Saed 2019). This process of gene mutation is part of the carcinogenic cascade initiated by inflammation.
7. Although the literature is still somewhat contradictory, aspirin and other non-steroidal anti-inflammatory drugs have been shown to prevent and treat certain types of cancer, particularly colorectal.(Trabert et al. 2019; Rayburn, Ezell, and Zhang 2009; Chan et al. 2005).

Inflammation/oxidative stress has been well established as a significant factor in the development of cancer, including ovarian cancer. Inflammation/oxidative stress facilitates cancer growth at multiple steps. Inflammation/oxidative stress is an early step in the molecular pathway by which talc causes ovarian cancer.⁷

IX. CORNSTARCH

Since 1948 with a publication from Johnson & Johnson's, own laboratory, it has been clear that starch is a safer alternative to talc for use on surgical gloves. Starch, unlike talc, is not an irritant and can be absorbed readily. (Eberl and George 1948).

A review paper by Whysner and Mohan in 2000 evaluated the available literature regarding the effects of cornstarch in the peritoneal cavity, comparing the potential risk of ovarian cancer with cornstarch versus talc. Unlike talc, the authors noted that 1) cornstarch is capable of being removed by physiologic processes from the peritoneal cavity, 2) cornstarch contains no asbestos, and 3) epidemiologic studies reviewed found no relationship between cornstarch powder use and ovarian cancer. The authors concluded that any increased risk for ovarian cancer as a result of perineal exposure to cornstarch was biologically implausible. (Whysner and Mohan 2000).

X. DETERMINING WHETHER A RISK FACTOR IS CAUSATIVE

Although Bradford Hill factors are primarily an epidemiologic tool, the general principles provide a framework for clinical doctors to assess whether diseases like cancer can be caused by a particular agent, condition, or practice. These considerations are the same as those that I apply regularly, both in my clinical practice and research.

The factors as described by Bradford Hill are:

1. Strength (effect size): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
2. Consistency (reproducibility): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
3. Specificity: Causation is more likely if there is a specific disease with no other likely explanation. Most frequently used example is a specific bacterium causing a particular disease (e.g. *M. tuberculosis* causes TB and *T. pallidum* causes syphilis). The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship, but this is not necessarily required.

⁷ Richard Zazenski, Director Product Safety for Luzenac, states in an email to Bill Ashton, on September 30, 2004: "I came across this paper this morning published in the April, 2004 journal "Human Reproduction", an official journal of the European Society for Human Reproduction and Embryology. It offers some compelling evidence **in support of the** 'migration' hypothesis. Combine this 'evidence' with the theory that talc deposition on the ovarian epithelium initiates epithelium inflammation – which leads to epithelium carcinogenesis – and you have a potential formula for NTP classifying talc as a causative agent in ovarian cancer." (IMERY5137677-IMERY5137690).

4. Temporality (and Latency): The effect must occur after the cause (and if there is an expectant delay between the cause and expected effect, then the effect must occur after that delay).
5. Biological gradient (Dose-response): Greater exposure should generally lead to greater incidence of the effect. There may also be a minimum level of exposure necessary (threshold). As a general principle of pharmacology and toxicology, the likelihood of a response increases with longer and more frequent exposure to an agent (dosage). (Klaassen and Doull 2013).
6. Plausibility: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism can be limited by current knowledge). Knowledge and an understanding of the biological mechanisms changes over time.
7. Coherence: Coherence between epidemiological and other research data/findings increases the likelihood of an effect. Coherence is the idea that an alleged association should not conflict with substantive knowledge that exists regarding the disease at issue.
8. Experiment: "Occasionally it is possible to appeal to experimental evidence". This factor often refers to support from animal and clinical research with sound methodology. Has there been an attempt to collect data to analyze a cause and effect relationship? Do studies use controls when feasible? Are experiments reproducible? Are there ethical limitations?
9. Analogy: The effect of similar factors may be considered. All the rules relating to scientific methodology must be employed at each stage of the analogy. (Fedak et al. 2015).

I considered these aspects of a causal relationship in determining whether talcum powder products cause ovarian cancer.

Strength

Overall the studies show a 1.3-1.4 odds ratio of increased risk of ovarian cancer among perineal talc users. The most recent and most complete meta-analysis determined an odds ratio of 1.31 with any perineal talc use and the development of ovarian cancer. An association with ever use of talc was found in case-control studies (OR = 1.35), but not cohort studies (OR = 1.06). However, cohort studies found an association between talc use and invasive serous type ovarian cancer (OR = 1.25). (Penninkilampi and Eslick 2018).

If invasive serous ovarian cancer is considered exclusively, the association is even stronger.

In general, many of the studies are well conducted, numerous and consistent, making the strength of the association valid. When looking at causation of a relatively rare disease like ovarian cancer, this magnitude of risk is statistically and clinically significant and not unusual. With ovarian cancer, a disease which is difficult to diagnose and deadly, any preventable risk factor (talcum powder) should be deemed critically important and avoided.

Consistency

The magnitude of risk has been consistent over three decades, across various geographic populations and throughout the United States, Canada, and Australia. Results are generally consistent across case-control, meta-analysis, and pooled analysis studies. (Penninkilampi and Eslick 2018). I deemed the consistency and replication of the studies to be important in my causation analysis.

Specificity

The most compelling disease associated with talcum powder use is epithelial ovarian cancer, therefore specificity for a disease is demonstrated.

Temporality

Exposure to talcum powder and the resultant development of ovarian cancer meets the temporality consideration that the outcome follows the event. The average latency period between exposure to talc and diagnosis of ovarian cancer is at least twenty years. This is consistent with other cancers known to be caused by chemicals and/or toxins. (Purdie et al. 2003; Okada 2007)

Biologic Gradient (Dose-response)

Exposure is difficult to quantify with talcum powder applications with regard to how much is used, where it is concentrated, and how much actually reaches the tubes and ovaries; Many of the studies did not obtain the necessary information to evaluate dose response and lacked adequate power to assess dose-response accurately. Despite the lack of sufficient information in many studies, recent meta-analyses/pooled study and a case-control studies do show a dose response, using frequency and duration of use as parameters. (Penninkilampi and Eslick 2018; Cramer et al. 2016; Schildkraut et al. 2016; Terry et al. 2013; A. H. Wu et al. 2015). Modern medicine also recognizes that a monotonic dose-response curve is often overly simplistic (e.g. asbestos demonstrates a threshold rather a linear dose-response). Response can vary based on unique characteristics of the given population, exposure routes, molecular endpoints, individual susceptibility and synergistic or antagonistic effects of cumulative exposures. (Fedak et al. 2015). Given the limitations of the data, I consider this a less important factor when compared to the strength of the association, consistency, and the biological mechanism.

Plausibility

The general mechanism by which talcum powder products cause ovarian cancer is established as an inflammation-induced process. It is well-accepted that particles reach the fallopian tubes and ovaries through migration/transport through the genital tract. These particles can also reach the pelvic organs through inhalation. The particles elicit an inflammatory tissue response and initiate a cascade of events and pathways at the cellular level that result in cancer formation. This process is well-described by the medical and scientific community. In addition, as previously discussed in this report, various components of talcum powder products, including asbestos and fibrous talc, are known carcinogens and known to cause cancer by similar mechanisms.

Coherence

The findings and conclusions from epidemiological, animal, and in vitro studies are coherent with what is known about ovarian cancer. There is also consistency with what is known about other gynecological malignancies and other cancers induced by environmental and occupational exposures.

Experiment

Causation of ovarian cancer by talcum powder is supported by laboratory (*in vitro* and *in vivo*) experiments. Research is ongoing which will further elucidate specific processes.

Prospective randomized controlled clinical trials to evaluate talcum powder products and their relationship to ovarian cancer are not feasible for a variety of ethical and methodological reasons. These include the recognized toxicity of talc, asbestos, and other constituents of talcum powder, the absence of therapeutic benefit, the long latency period, and the seriousness of ovarian cancer.

Analogy

As with consistency, plausibility, and coherence, the association between talcum powder and ovarian cancer is analogous to other diseases caused by various and specific carcinogens. For example, smoking causes lung cancer, asbestos causes mesothelioma and ovarian cancer, sun exposure causes skin cancer, and HPV causes cervical cancer. All of these cancers are the result of an inflammatory process initiated by a foreign agent.

XI. SUMMARY OF OPINIONS

The opinions in this report are provided to a reasonable degree of medical and scientific certainty. A summary of these opinions follows:

1. Based on epidemiological studies, the established biological mechanism, and evidence of the presence of asbestos and other known carcinogens, talcum powder products cause epithelial ovarian cancer in some women. The genital use of talcum powder products presents a significant risk factor for ovarian cancer for *all* women who use the products.
2. When looking at epidemiological studies in their totality, the data demonstrates a consistent, replicated, and statistically significant increased risk of developing epithelial ovarian cancer with perineal talcum powder use.
3. Asbestos is one of the most potent human carcinogens and known to cause ovarian cancer. The presence of asbestos in talcum powder products contributes to their carcinogenicity. In addition, other known constituents of talcum powder products (including nickel, chromium, and cobalt) are carcinogenic and their presence likely contributes to the cancer-causing properties of talcum powder products.

4. The extensive number of fragrance chemicals added to the talcum powder products likely contributes to the inflammatory properties, toxicity, and carcinogenicity of these products.
5. The migration/transport of particles, including talc and asbestos, to the upper genital tract (tubes and ovaries) is a key element in the mechanism by which talcum powder products cause ovarian cancer. The evidence supporting migration is robust and universally accepted by the gynecologic community. In addition to perineal application resulting in migration and transport of particles through the genital tract, inhalation of these particles is another recognized route of exposure.
6. Inflammation/oxidative stress is an early and essential step in the molecular process by which talcum powder products cause ovarian cancer.
7. Cornstarch is a safer alternative to talcum powder.
8. Talcum powder use is a preventable causative risk factor for EOC.

Based on my education, training, experience and expertise in ovarian and other gynecologic cancers, review of the totality of the evidence, analysis and weighing the data in the context of Bradford Hill, it is my professional opinion that talcum powder products cause epithelial ovarian cancer in some women. The use of talcum powder products presents a significant risk factor for ovarian cancer in *all* women who use the products.

I reserve the right to amend or modify the report as new information becomes available.

I have not testified in litigation over the previous 4 years. I am charging \$600 per hour for my work on this matter.

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Exhibit A

CURRICULUM VITAE

Judith K Wolf, MD

PRESENT TITLE AND AFFILIATION

**Chief Medical Officer
ProvistaDx
55 Broad St 18th Floor
New York, NY 0004**

CITIZENSHIP

United States

OFFICE ADDRESS

**ProvistaDx
55 Broad St 18th Floor
New York, NY 0004**

PREVIOUS WORK EXPERIENCE

Chief Medical Officer

Vermillion, Inc

12117 Bee Caves Rd

Austin TX 78738

9/2014-6/2016

Division Chief of Surgery

Banner MD Anderson Cancer Center

**2946 E Banner Gateway Dr
Gilbert, AZ 85235**

6/2011-9/2014

Faculty

The University of Texas MD Anderson Cancer Center

1515 Holcombe Blvd

Houston, TX 77030

7/1995-6/2011

EDUCATION

Degree-Granting Education

University of Akron, Akron, OH, BS, 1982, Natural Sciences

Northeastern Ohio Universities College of Medicine, Rootstown, OH, MD, 1986, Biomedical Science

The University of Texas Health Science Center at Houston, Houston, TX, MS, 1993, Biomedical Sciences- Thesis, Characterization of two populations of the human ovarian cancer cell line, 2774, that express different levels of epidermal growth factor receptor.

Postgraduate Training

Residency, Obstetrics and Gynecology

U.T. Health Science Center at San Antonio, San Antonio, TX, Dr. Carl J. Pauerstein

1986-1990

Fellowship, Gynecologic Surgery

University of Minnesota, Duluth, MN, Dr. Leo Twiggs

1990-1991

Fellow, Gynecologic Oncology, Department of Biology

The University of Texas MD Anderson Cancer Center, Houston, TX, Dr. J Taylor Wharton 1991-1993

Junior Faculty Associate, Gynecologic Oncology The University of Texas MD Anderson Cancer Center, Houston, TX, Dr. J. Taylor Wharton 1993-1995

CREDENTIALS

Board Certification

American Board of Obstetrics and Gynecology, (Written Exam), 1990

American Board of Obstetrics and Gynecology: Special Qualification in Gynecologic Oncology, (Written Exam), 1996

American Board of Obstetrics and Gynecology, 1997

-Recertified 2014

American Board of Obstetrics and Gynecology: Special Qualification in Gynecologic Oncology, 2000

-Recertified 2014

Licensures

Active

State of Arizona, AZ, 45110, 7/2011 – current

State of Indiana, IN 01074549B, 9/2014- current

State of Georgia, GA 173182 6/2014- present

Inactive

State of Minnesota, MN, 1/1990–1/1993

State of Texas, TX, H4856, 1988–8/2012

EXPERIENCE/SERVICE

Academic Appointments

Assistant Professor, Department of Gynecologic Oncology, Division of Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 1995–1999

Assistant Professor, Department of Gynecologic Oncology, Division of Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 1999–2002

Associate Professor, Department of Gynecologic Oncology, Division of Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 2002–8/2008

Graduate Faculty, Biomedical Sciences, Graduate School of Biomedical Sciences, The University of Texas Houston Health Science Center, Houston, TX, 2003–2011

Associate Professor, Department of Gynecologic Oncology, Blanton Davis Ovarian Cancer Research Program, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 2006–8/2008

Associate Director, Department of Gynecologic Oncology, Developmental Therapeutics,

The University of Texas MD Anderson Cancer Center, Houston, TX, 2006–2011

Co-Division Director, Department of Gynecologic Oncology, Division of Surgery, Baylor College of Medicine, Houston, TX, 4/2006–4/2007

Professor, Department of Gynecologic Oncology, Blanton Davis Ovarian Cancer Research Program, The University of Texas MD Anderson Cancer Center, Houston, TX, 2008–2011

Associate Director, Department of Gynecologic Oncology, Developmental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, 2011

Division Chief, Surgical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ 6/2011–9/2014

Vice Chair, Department of Oncology Services, Banner MD Anderson Cancer Center, Gilbert, AZ 6/2011–/9-2014

Adjunct Professor, Gynecologic Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas, 2012– 2014

Clinical Professor, Division of Clinical Education, Arizona College of Osteopathic Medicine, Midwestern University, Arizona, 2012– 2014

Administrative Appointments/Responsibilities

Assistant Program Director (Research), Fellowship in Gynecologic Oncology, Division of Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 1999–2004

Medical Director, Community Relations, Department of Gynecologic Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, 4/2008–2011

Other Appointments/Responsibilities

Member, Felix Rutledge Society, Houston, TX, 1995–Present

President, Felix Rutledge Society, 2008–2009

Member, Society of Gynecologic Oncologists, Chicago, IL, 1996–Present

Member, Quality and Outcomes Committee, Society of Gynecologic Oncology, 2012–Present

Member, Breakthrough Series: Improving Care at the End of Life, Houston, TX, 1997–2011

Founder-Chairman, Sprint for Life 5K Fun Run, M. D. Anderson Cancer Center, Houston, TX,
1998–Present

Chairman, Medical and Scientific Advisory Board, National Ovarian Cancer Coalition, Dallas, TX,
2003–Present

President, Houston Gynecologic & Obstetrics Society, Houston, TX, 2003–2004

Treasurer, Houston Gynecologic & Obstetrics Society, Houston, TX, 1998–2000

Vice President, Houston Gynecologic & Obstetrics Society, Houston, TX, 2001–

Member, Gynecologic Oncology Group, Philadelphia, PA, 2001–2011

Departmental Liaison, M D Anderson Cancer Center Women Faculty Programs, Houston, TX,
2/2010–2011

Endowed Positions

N/A

Consultantships

N/A

Military or Other Governmental Service

N/A

Institutional Committee Activities

Medical Records Committee, Member, 1995–2011

Clinical Research Committee, Member, 1997–2000

Women's Faculty Administrative Organization Steering Committee, Member, 1998–1999

Cancer Committee, Hermann Hospital, Member, 1998–2001

Search Committee, Anesthesia, Member, 1999–2000

Ovarian SPORE Executive Committee, Member, 1999–2011

Student and Trainee Resources-Clinical Fellow's Research Award, Faculty Reviewer, 1999

Cancer Therapeutics Discovery Program Grants, Reviewer, 2000–2004

Clinical Research Committee, Member, 2001–2004

Search Committee, Internal Medicine, Member, 2001

Uterine SPORE Executive Committee, Member, 2003–2011

Faculty Promotion and Tenure Committee, Division of Surgery, Member, 2003–2011

Gynecologic Oncology Surgical Research Program (GO-SRP) Committee, Member, 2004–2011

Fellowship Planning Committee, Member, 2004–2011

Blanton-Davis Ovarian Cancer Research Program Executive Committee, Member, 2004–2011

Faculty Celebration Steering Committee, Member, 2004

Gynecologic Oncology Center for Surgical Research (GOCSR), Member, 2004

Ovarian Working Group, Department of Gynecologic Oncology, Chairman, 2005–2011

Search Committee, Department of Nephrology Chair, Member, 2005

Gynecologic Oncology T32 - Program Steering Committee, Member, 2005

The University of Texas M. D. Anderson Cancer Center, Gynecologic Oncology Group (GOG), Co-Principal Investigator, 2005–2011

Faculty Celebration Gala, Chairman, 2005

Faculty Leadership Committee, Member, 2006–2011

Executive Committee of Faculty Senate, Member, 2007–2009

Faculty Senate Committee, Chair Elect, 2010–2011

Faculty Senate Committee, Chair, 2011 – 2012

Faculty Senate Committee, Member, 2006–2011

Gynecologic Oncology Committee for New Institute of Personalized Cancer Therapy, Head, 4/2008–2011

Award Nomination Selection Committee, 2010–2011

Clinical Research Counsel, Member, 6/2008–2011

Clinical Research Committee, Member, 7/2009–2011

Women Faculty Programs, Member, 8/2009–2011

Charitable Activities Committee Subcommittee, Member, 2010–2011

OPPE/FPPE, Department Safety Officer, 2/2010–2011

Institutional Review Board 1 (IRB1), Associate Member, 8/2010–2011

Vice Chair, Department of Oncology Services, BMDACC, 2011– 2014

BMDACC Perioperative Logistic Committee, 2011– 2014

BMDACC Surgery Committee, 2011– 2014

BMDACC Phase II Steering Committee, 2011–2014

Relationship Committee between UT MD Anderson Cancer Center and BMDACC, 2011– 2014

BMDACC Research Faculty Guidance Committee, 2011– 2014

Banner Medical Group Knowledge Management Committee, 2012– 2014

BMDACC, Affiliate of UTMDACC for Gynecologic Oncology Group (GOG), Principal Investigator, 2012–
2014

BMDACC Biospecimen Governance Committee Chair 2013- 2014

BMDACC Research Committee, Co-chair 03/2013- 2014

Banner Health Oncology Steering Committee, 5-9/2014

HONORS AND AWARDS

Medical Honor Society, Alpha Omega Alpha, 1986

Galloway Fellowship in Gynecologic Oncology, Memorial Sloan Kettering Cancer Center, 1989

Best Doctors in America®, 2005–2006, 2006–2007, 2007–2008, 2011, 2013

RESEARCH

Grants and Contracts (past 5 years)

Funded

Principal Investigator-MDACC, J. S. Blanton Research Fund, J. S. Blanton Research Fund, 1999–2011, \$116,367

Principal Investigator, 10%, Gene Developmental in Ovarian Cancer, Specialized Program of Research Excellence, 2001– 2011, \$50,000

Principal Investigator, Gene Therapy Development Award, W. M. Keck Center for Cancer Gene Therapy Development Award, 2001– 2011, \$50,000

Principal Investigator, Texas Federation of Business Professional Women Award, Texas Federation of Business Professional Women Award, 2001– 2011, \$6,337

Principal Investigator, The Ovarian Cancer Survivors Fund, Don-Ray George & Associates, 2003 – 2011, \$116,126

Co-Investigator, Efficacy and Mechanism of SERMs for Recurrent / Advanced Endometrial Cancer, Molecular Progression of Endometrial Cancer, P150CA098258, Specialized Program of Research Excellence, PI - Karen H. Lu, 9/1/2003 – 8/31/2008, \$992,019

Principal Investigator-MDACC, Gynecologic Oncology Center for Surgical Research (GOCSR), Houston Jewish Community Foundation, 2004 – 2011, \$50,000

Principal Investigator-MDACC, Susan G. Koch Ovarian Cancer Research Fund, Susan G. Koch, 2005 – 2011, \$50,000

Co-Investigator, The University of Texas M D Anderson Cancer Center, Gynecologic Oncology Group, Gynecologic Oncology Group, PI - Robert Coleman, M.D., 2005 – 2011.

Pending

N/A

Other

N/A

Completed

Principal Investigator, Evaluation of the Effect and Mechanism of Action of Adenovirus-mediated Tumor Suppressor Gene Therapy of Ovarian Cancer, Gynecologic Cancer Foundation, 1998–2006, \$25,000

Co-Investigator, Evaluating Fatigue and Other Symptoms of Ovarian cancer Patients with Ecological Momentary Assessment, Ovarian Cancer Research Development Award, PI - Karen Basen Engquist, Ph.D., 1999–2006, \$50,000

Not Funded

N/A

Protocols

Funded

Principal Investigator, Evaluating Fatigue and Other Symptoms of Ovarian Cancer Patients with Ecological Momentary Assessment, ID99-, 1999, Ovarian Cancer Research Development Award

Principal Investigator, A Phase II Study of Oral Xeloda Administered Twice Daily for Fourteen Days Every Three Weeks to Patients with Advanced Ovarian, Tubal or Peritoneal Cancer Refractory to Platinum and Taxanes, GYN 00-275, 2000–2001

Co-Principal Investigator, Phase II Evaluation of Oxaliplatin In Persistent or Recurrent Squamous Cell Carcinoma of the Cervix, GOG127P, PI - Charles Levenback, 2000–2003, GOG

Principal Investigator, A Phase 1 Dose Escalation Study of Intraperitoneal E1A Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer, ID 99-316, 2000–2006

Co-Principal Investigator, A Phase II Evaluation of Thalidomide (NSC #66847, IND #48832) In the Treatment of recurrent or Persistent Leiomyosarcoma of the Uterus, GOG231B, PI - Diane Bodurka, 2001–2002, GOG

Co-Principal Investigator, A Phase II Multicenter Study of Oral Xeloda Administered Twice Daily for Fourteen Days Every Three Weeks to Patients with Advanced or Recurrent Cervical Cancer, GYN01-080, PI - Lois Ramondetta, M.D., 2001–2003

Collaborator, A 2-Part Phase I/II Study of Extended Field External Irradiation and Intracavitary Brachytherapy combined with Chemo (Weekly Cisplatin-Arm 1) and Amifostine (Weekly Cisplatin and Amifostine-Arm 2), RTOG-C0116, PI - Anuja Jhingran, M.D., 2001– 2011, RTOG

Principal Investigator, A Phase I/II Study to Evaluate the Maximum Biologic Dose of Pegylated-Interferon (PEG- INTRON) in Patients with Platinum Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer, ID02-115, 2002–2005, \$100,000, Integrated Therapeutics Group/Schering Plough

Collaborator, A Phase II Evaluation of Decetaxel and Gemcitabine Plus G-CSF in the treatment of recurrent of Persistent Leiomyosarcoma of the Uterus, GOG-0131G, PI - Lois Ramondetta, M.D., 2002–2005, GOG

Collaborator, A Phase II Evaluation of Liposomal Doxorubicin (Doxil) in the Treatment of Persistent or

Recurrent Squamous Cell Carcinoma of the Cervix, GOG 127-R, PI - Diane Bodurka, M.D., 2002–2005, GOG

Co-Principal Investigator, Phase II Study of Irofulven (IND #48914) in Patients with Refractory or Recurrent Advanced Epithelial Ovarian Cancer Using Every-Other-Week Dosing, GYN01-486, PI - Diane Bodurka, 2002–2005

Collaborator, A Phase II Evaluation of Capecitabine (NSC#712807) in the Treatment of Persistent or Recurrent Non-squamous Cell Carcinoma of the Cervix, GOG-0128G, PI - Diane Bodurka, M.D., 2002–2011, GOG

Collaborator, Treatment of Patients with Stage IB2 Carcinoma of the Cervix: A Randomized Comparison of Radical Hysterectomy and Tailored Chemo-Radiation versus Chemo-radiation, GOG0201, PI - Charles Levenback, M.D., 2003–2005, GOG

Collaborator, A Randomized Study of Tamoxifen versus Thalidomide (NSC no.66847) in Patients with Biochemical-Recurrence- Only Epithelial Ovarian Cancer of the Fallopian Tube, and Primary Peritoneal Carcinoma after First-Line Chemotherapy, GOG-0198, PI - Robert Coleman, M.D., 2003–2006, GOG

Collaborator, A Phase I/II Study of COX-2 Inhibitor, Celebrex (Celecoxib), and Chemoradiation in Patients with Locally Advanced Cervical Cancer, RTOG-C0128, PI - Patricia Eifel, M.D., 2003–2011, RTOG

Principal Investigator, A Phase I/II Study of Gleevec/Taxol in Patients with Newly Diagnosed Stage IIIC or IV or Recurrent (any stage) Uterine Papillary Serous Carcinoma (UPSC), GYN03-0177, 2003–2011, Novartis

Collaborator, A Phase III Clinical Trial of Tisseel VH Fibrin Sealant to Reduce Lymphedema Incidence after Inguinal Lymph Node Dissection Performed in the Management of Vulvar Malignancies, GOG195, PI - Pedro Ramirez, M.D., 2003–2011, GOG

Collaborator, A Phase III Randomized Clinic Trial of Laparoscopic Pelvic & Para-Aortic Node Sampling with Vaginal Hysterectomy and BSO versus Open Laparotomy with Pelvic and Para-Aortic Node Sampling and Abdominal Hysterectomy and BSO in Endometrial Adenocarcinoma and Uterine Sarcoma, GOG-LAP2, PI - Pedro Ramirez, M.D., 2003–2011, GOG

Collaborator, A Phase III Randomized Trial of Paclitaxel and Carboplatin versus Triplet or Sequential Doublet Combinations in Patients with Epithelial Ovarian or Primary Peritoneal Cancer, GOG-0182, PI - John Kavanagh, M.D., 2003–2011, GOG

Collaborator, A Randomized Phase III Study of Paclitaxel plus Cisplatin versus Vinorelbine Plus Cisplatin versus Gemcitabine Plus Cisplatin versus Topotecan Plus Cisplatin in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix, GOG-0204, PI - Charles Levenback, M.D., 2003–2011, GOG

Principal Investigator, Phase I/II Study of Weekly Topotecan and Iressa in Patients with Platinum-Resistant Ovarian/Peritoneal/Fallopian Tube Cancer, 2003-0322, 2004–2007, \$92,500, GlaxoSmithKline/Astra Zeneca

Principal Investigator, A Phase I/II Randomized Study of Intraperitoneal tgDCC-E1A and Intravenous Paclitaxel in Women with Platinum-Resistant Ovarian Cancer, ID02-321, 2004–2011, \$365,000, Marcus Foundation Funds-UT M. D. Anderson Cancer Center

Principal Investigator, A Phase II Study of RAD001 in Patients with Recurrent Endometrial Cancer, 2004-0002 IND 69277, 2004–2011, \$111,300, Novartis

Collaborator, A Randomized, Phase II Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF versus Carboplatin/Paclitaxel in Patients with Stage III and IV or Recurrent Endometrial Cancer, GOG-0209, PI - Lois Ramondetta, M.D., 2004–2011, GOG

Mentor, Training Grant - Department of Gynecologic Oncology, Training of Academic Gynecologic Oncologists, NIH/NCI, 1 T32CA101642-01A, PI - David M. Gershenson, MD, 2005–2010, \$1,535,549 (\$181,757/year), NIH/NCI

Collaborator, A Limited Access Phase II Trial of Cetuximab (C225, NSC 714692) in Combination with Cisplatin (NSC #119875) in the Treatment of Advanced, Persistent, or Recurrent Carcinoma of the Cervix, GOG-0076DD, PI - Robert Coleman, M.D., 2005–2011, GOG

Principal Investigator, A Phase I Trial of Tailored Radiation Therapy with Concomitant Cetuximab (C225, NSC# 714692) and Cisplatin (NSC# 119875) in the Treatment of Patients with Cervical Cancer, GOG-9918, 2005–2011, GOG

Collaborator, A Phase II Evaluation of Pemetrexed (Alimta, LY231514, IND #40061) in the Treatment of Recurrent Carcinoma of the Cervix, GOG-0127T, PI - Charles Levenback, M.D., 2005–2011, GOG

Collaborator, A Phase II Evaluation of Thalidomide (NSC# 66847, IND# 48832) In The Treatment Of Recurrent Or Persistent Carcinosarcoma of the Uterus, GOG-0230B, PI - Lois Ramondetta, M.D., 2006–2007, GOG

Principal Investigator, A Dose-Escalating Phase I Study with an Expanded Cohort to Assess Feasibility of Intraperitoneal Carboplatin & Intravenous Paclitaxel in Patients with Previously Untreated Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer, GOG-9917, 2006–2011, GOG

Collaborator, A Phase II Evaluation of Pemetrexed (Alimta, LY231514, IND #40061) in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma, GOG-0126Q, PI - Siqing Fu, M.D., 2006–2011, GOG

Co-Principal Investigator, A Phase II Study of Faslodex in Recurrent/Metastatic Endometrial Carcinoma, GOG-0188, PI - Lois Ramondetta, M.D., 2006–2011, GOG

Co-Principal Investigator, Phase III Carboplatin & Paclitaxel + Placebo vs. Carboplatin & Paclitaxel + Concurrent Bevacizumab (NSC #704865, IND # 7921) follow by Placebo, vs Carboplatin & Paclitaxel + Concurrent & Ext Bevacizumab, in Advanced Stage Epithelial Ovarian & Peritoneal Primary Cancer, GOG-0218, PI - Robert Coleman, M.D., 2006–2011, GOG

Collaborator, A Phase II Evaluation of ABI-007 (IND #55,974) in the Treatment of Persistent or Recurrent Squamous or Non Squamous Cell Carcinoma of the Cervix (Abraxis BioScience, Inc. Study #CA026) (Group B), GOG-0127V, PI - Robert Coleman, M.D., 2007–2011, GOG

Principal Investigator, Preliminary Evaluation of Femara (Letrozole) for Adjuvant Treatment After Completion of First-Line Chemotherapy for Patients with Optimally Debulked and Chemosensitive Ovarian Cancer, IRB 2006-0689, 2007–2011, \$314,989

Principal Investigator, Randomized Phase 2 Study of MLN8237, an Aurora A Kinase Inhibitor, Plus Weekly Paclitaxel or Weekly Paclitaxel Alone in Patients with Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, Preceded by a Phase 1 Portion in Patients with Ovarian or Breast Cancer, Millennium.

Unfunded

Collaborator, A Phase II Study of Intravenously Administered Tirapazamine Plus Cisplatin in Subjects with Cervical Cancer, GYN96-136, PI - Charles Levenback, M.D., 1996-2004

Principal Investigator, Phase I Study of recurrent ovarian cancer Adp53, ID 97-288, 1997

Collaborator, Telomerase Testing in Peritoneal Washings from Ovarian Cancer Patients Undergoing Second Look Laparotomy, LAB98-080, PI - David Gershenson, M.D., 1998-2005

Collaborator, A Pilot Study of Transfusion of rhTPO-Derived Autologous Platelets Cryopreserved with Thrombocytol and 2% DMSO in Patients with Gynecologic Malignancy Receiving Carboplatin, GYN97-310, PI - Saroj Vadhan, 1999-2004

Collaborator, Paclitaxel, Carboplatin, and Herceptin for Patients with Untreated Advanced, (Cohort A) or Recurrent Platinum-Sensitive (Cohort B) Epithelial Ovarian Cancer, Peritoneal Cancer, or Fallopian Tube Cancer, GYN99-067, PI - David Gershenson, M.D., 1999-2004

Collaborator, Paclitaxel, Carboplatin, and Herceptin for Patients with Untreated Advanced Epithelial Ovarian Cancer, Peritoneal Cancer, or Fallopian Tube Cancer, GYN99-132, PI - David Gershenson, M.D., 1999-2007

Collaborator, Feasibility of Measuring Gene Expression Patterns Using Tissue Acquisition of Primary Stage III and IV Epithelial Ovarian Cancer, Fallopian Tube, or Primary Peritoneal Cancer and Gene Expression Array Technology for Predicting Paclitaxel Chemotherapy Sensitivity and Resistance, ID00-408, PI - David Gershenson, M.D., 2000-2011

Principal Investigator, Phase II Study of Paclitaxel for Ovarian Stromal Tumors as First-Line or Second-Line Therapy, GOG-0187, 2000

Collaborator, A Phase II Study of Intraperitoneal E1A-Lipid complex for Patients with Advanced Epithelial Ovarian CX without Her-2/Neu Overexpression, ID00-306, PI - Naoto Ueno, 2001-2002

Collaborator, Phase II Study of Intraperitoneal Recombinant Human Interleukin-12 (RHIL-12) in Patients with Peritoneal Carcinomatosis (Residual Disease <1cm) Associated with Ovarian epithelial CX or Primary Peritoneal Carcinoma, ID00-232, PI - Renato Lenzi, 2001-2005

Collaborator, Feasibility Study of Intraoperative Lymphatic Mapping and Sentinel Lymph Node Identification in Patients with Endometrial Cancer, ID01-290, PI - Diane Bodurka, M.D., 2001-2006

Collaborator, A Phase II Multicenter Trial of Paclitaxel and Carboplatin in Women with Advanced (IIb, IIc, IVa and IVb) or Recurrent (All Stages) Mixed Malignant Mullerian Tumors (MMMT) of the Uterus, ID01-229, PI - Lois Ramondetta, M.D., 2001-2011

Collaborator, A Phase II Study: Paclitaxel and Pelvic Radiation for Stage I-IIIa Papillary Serous Carcinoma of the Endometrium, ID-418, PI - Anuja Jhingran, 2001-2011

Collaborator, Chemotherapy-Related Toxicities in Ovarian Cancer Patients: Preference Assessments of Patients, Family Members, Ancillary Staff and Gynecologic Oncologists, and Patients' Quality of Life, GYN00-409, PI - Diane Bodurka, M.D., 2001-2011

Collaborator, Clinical and Molecular Genetic Determinants of Late Complication in Patients Treated with Radiation Therapy for Cervical Cancer, LAB01-380, PI - Patricia Eifel, M.D., 2001-2011

Collaborator, Evaluating Fatigue and Other Symptoms of Ovarian Cancer Patients with Ecological Momentary Assessment, ID00-013, PI - Karen Basen-Engquist, 2001-2011

Collaborator, Phase II Study of Mifepristone (RU-486) in the Treatment of PR Positive Advanced/Recurrent Endometrial Adenocarcinoma and Low Grade Endometrial Stromal Sarcoma (LGES), ID01-212, PI - Lois Ramondetta, M.D., 2001-2011

Collaborator, Use of the CA125 Algorithm for the Early Detection of Ovarian Cancer in Low Risk Women, ID01-022, PI - Karen Lu, 2001-2011

Co-Principal Investigator, Vacuum-Assisted Closure in the treatment of Gynecologic Oncology Wound Failures, RCR01-156, PI - Pedro Ramirez, 2002-2003

Collaborator, Phase I Trial of Concurrent Weekly CPT-11, Cisplatin, and Radiotherapy for Patients with Newly Diagnosed Stage IIb-IVa Cancer of the Uterine Cervix, ID02-526, PI - Pedro Ramirez, M.D., 2002-2005

Collaborator, A Phase II Study of Chemoimmunotherapy for Patients with Potentially Platinum Sensitive Müllerian (Epithelial Ovarian, Peritoneal, or Fallopian Tube) Carcinomas, ID02-231, PI - Ralph Freedman, M.D., Ph.D., 2002-2011

Collaborator, A Prevalence Study of HNPCC Gene Mutation in Women with Endometrial Cancers, ID01-533, PI - Karen Lu, M.D., 2002-2011

Collaborator, Feasibility of Measuring Gene Expression Patterns Using Tissue Acquisition of Primary Peritoneal CX and Gene Expression Array Technology for Predicting Paclitaxel Chemo Sensitive and Resistant, ID00-408, PI - David M. Gershenson, M.D., 2002-2011

Collaborator, Modulation of Putative Surrogate Endpoint Biomarkers in Endometrial Biopsies from Women with HNPCC, ID01-340, PI - Karen Lu, M.D., 2002-2011

Collaborator, The Utility and Impact of Computed Tomography and Serum CA-125 in the Management of Newly Diagnosed Ovarian Cancer, ID02-143, PI - Pedro Ramirez, M.D., 2002-2011

Co-Principal Investigator, Evaluation of Molecular Markers in Malignant Mixed Mesodermal Tumors (MMMT) of the Ovary, LAB03-0653, PI - Lois Ramondetta, M.D., 2003-2005

Co-Principal Investigator, A Phase I Study Evaluating the Safety and Tolerability of PS-341(Bortezomib) and Carboplatin in Patients with Platinum Resistant Recurrent Ovarian Cancer, Primary Peritoneal Cancer, and Fallopian Tube Cancer, ID02-114, PI - Pedro Ramirez, 2003-2007

Collaborator, Phase III Randomized Study of TLK286 Versus Doxil/Caelyx or Hycamtin as Third-Line Therapy in Platinum Refractory or Resistant Ovarian Cancer, ID03-184, PI - John Kavanagh, M.D., 2003-2007
Co-Principal Investigator, Role of Secondary Cytoreductive Surgery for Recurrent Ovarian: A 20-Year Experience, RCR03-0803, PI - Pedro Ramirez, 2003-2007
Collaborator, A Phase II Study Evaluating the Utility of Letrozole in the Treatment of Recurrent, Estrogen Receptor (ER) Positive, Epithelial Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer, ID02-698, PI - Pedro Ramirez, M.D., 2003-2011
Collaborator, A Pilot Study of Laparoscopic Extraperitoneal Lymph Node Dissection in Patients with Locally Advanced Cervical Cancer, ID03-0098, PI - Pedro Ramirez, M.D., 2003-2011
Collaborator, Phase 1-2a Dose-Ranging Study of TLK286 in Combination with Doxil in Platinum Refractory or Resistant Ovarian Cancer, ID02-571, PI - John Kavanagh, M.D., 2003-2011
Collaborator, Phase II Study of Letrozole in Patients with Recurrent Advanced Borderline Tumors or Low Grade Epithelial Cancers of the Ovary, Fallopian Tube and Primary Peritoneum, 2003-0486, PI - John Kavanagh, M.D., 2003-2011
Collaborator, Quality of Life and Preferences of Ovarian Cancer Patients Enrolled on a Randomized Trial of High-Dose versus Conventional Dose Chemotherapy, ID02-680, PI - Charlotte Sun, Ph.D., 2003-2011
Co-Principal Investigator, A Phase II Study of Gemcitabine and Cisplatin for Advanced or Recurrent Endometrial Cancer, 2003-0823, PI - Jubilee Brown, M. D., 2004-2011
Collaborator, Chemoradiation-Induced Nausea and Emesis: A Prospective Study to Assess Patient Preferences and Quality of Life, 200-0529, PI - Charlotte Sun, Ph.D., 2004-2011
Collaborator, The Role of Appendectomy at the Time of Tumor Reductive Surgery in Patients with Epithelial Ovarian Cancer, RCR05-0630, PI - Pedro Ramirez, M.D., 2005
Collaborator, Total Laparoscopic Radical Hysterectomy: Outcomes Evaluation, RCR05-0390, PI - Pedro Ramirez, M.D., 2005-2007
Co-Principal Investigator, A Pilot Clinical Trial with Molecular Marker Study of Chemosensitization to Carboplatin by Use of Vidaza in Platinum Resistant or Refractory Epithelial Ovarian Cancer, 2005-0009, PI - Siqing Fu, M.D., 2005-2011
Collaborator, Evaluation of Demographics and Perioperative Care of Patients Undergoing Laparoscopic Surgery for Gynecologic Malignancies: A 15-Year Experience, RCR05-0137, PI - Pedro Ramirez, M.D., 2005-2011
Collaborator, Systemic Antineoplastic Therapy in Ovarian Cancer Patients with Renal Dysfunction, RCR05-0707, PI - John Kavanagh, M.D., 2005-2011
Collaborator, A Phase I Dose Escalation Study of ABI-007 with Carboplatin as First-Line Therapy in Patients with Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma, 2006-0405, PI - Robert Coleman, M.D., 2006-2011
Principal Investigator, Phase II Study of Cetuximab (Erbix) in Patients with Progressive or recurrent Endometrial Cancer, 2006-0211, 2006-2011
Collaborator, A Multi-Institutional Study of Proteomic Evaluation of Epithelial Ovarian Cancer, Primary Peritoneal Cancer, and Fallopian Tube Cancer Patients in First Clinical Remission: Development of a Protein Fingerprint Profile of Relapse, 2005-0780, PI - Karen Lu, M.D., 2007-2011
Co-Principal Investigator, A Phase II, Open-Label, Non-Comparative, International, MC Study to Assess the Efficacy and Safety of KU-0059436 Given Orally Twice Daily in Patients with Advanced BRCA1-or BRCA2-Associated Ovarian Cancer, 2007-0098, PI - Karen H. Lu, M.D., 2007-2011
Collaborator, A Study of the Efficacy of MORAb-003 in Subjects with Platinum-Sensitive Epithelial Ovarian Cancer in First Relapse, 2006-0889, PI - Robert Coleman, M.D., 2007-2011
Collaborator, Phase I/II and Pharmacokinetic Study of Docetaxel Plus VEGF Trap (AVE0005, NSC #724770) In Patients with Recurrent Ovarian, Primary Peritoneal, and Fallopian Tube Cancer, 2006-0329, PI - Robert Coleman, M.D., 2007-2011

Patents and Technology Licenses

Patents

N/A

Technology Licenses

N/A

Grant Reviewer/Service on Study Sections

Review Committee on NIH CTRC, NIH, Member, Louisiana State University, 1997
AD HOC on NCI P01, NCI, Ad Hoc Member, Tulane University Health Science Center, 2004
Clinical Research Review Committee NCI, NCI, Member, Mayo Clinic, 2004
NIH-CONC Clinical Oncology Study Section Review (R01, R21), NIH, Member, Clinical Oncology Study Section Review (R01, R21), San Francisco, CA, 2004
Review Committee NCI-NIH, NIH, Member, Duke Comprehensive Cancer Center, Duke University, 2004
Review Committee on NCI-I Career Awards, NCI, Member, 2004
NCI P01 Cluster Review, NIH, Member, Bethesda, MD, 2005
NIH-CONC Clinical Oncology Study Section Review (R01, R21), NIH, Member, Clinical Oncology Study Section Review (R01, R21), Bethesda, MD, 2005
Review Committee NCI-NIH, P01 Experimental Therapeutics II Cluster Review, NIH, Member, P01 Experimental Therapeutics II Cluster Review, Rockville, MD, 2005

PUBLICATIONS

Peer-Reviewed Original Research Articles

1. Yu D, **Wolf JK**, Scanlon M, Price JE, Hung MC. Enhanced c-erbB-2/neu expression in human ovarian cancer cells correlates with more severe malignancy that can be suppressed by E1A. *Cancer Res* 1993 Feb 15;53(4):891-8.
2. Hamada K, Zhang WW, Alemany R, Roth JA, **Wolf JK**, Mitchell MF. Gene therapy of cervical cancer by adenovirus-mediated p53 gene transfer. *J Cell Biochem Suppl* 1995; 21A:421.

3. Gershenson DM, Morris M, Burke TW, Levenback C, **Wolf JK**, Warner D, Matthews CM, Wharton JT. Treatment of poor-prognosis sex cord-stromal tumors of the ovary with the combination of bleomycin, etoposide, and cisplatin(BEP). *Obstet Gynecol* 1996 Apr;87(4):527-31.
4. **Wolf JK**, Levenback C, Malpica A, Morris M, Burke T, Mitchell MF. Adenocarcinoma in situ of the cervix: significance of cone biopsy margins. *Obstet Gynecol* 1996 Jul; 88(1)(1):82-6.
5. Levenback C, Morris M, Burke TW, Gershenson DM, **Wolf JK**, Wharton JT. Groin dissection practices among gynecologic oncologists treating early vulvar cancer. *Gynecol Oncol* 1996 Jul; 62(1)(1):73-7.
6. Hamada K, Zhang WW, Alemany R, **Wolf JK**, Roth JA, Mitchell MF. Growth inhibition of human cervical cancer cells with recombinant adenovirus p53 in vitro. *Gynecol Oncol* 1996;60(3):373-379.
7. Mitchell MF, Hamada K, Jagannadha S, Satterfield WC, Buchholz S, **Wolf JK**, Zhang WU, Alemany R, Tortolero-Luna G, Keeling ME, Wharton JT, Roth JR. Transgene expression in the rhesus cervix mediated by an adenovirus expressing b-galactosidase. *Am J Obstet Gynecol* 1996;174:1094-1101.
8. Brader KR, **Wolf JK**, Hung MC, Yu D, Crispens MA, van Golen KL, Price JE. Adenovirus E1A expression enhances the sensitivity of an ovarian cancer cell line to multiple cytotoxic agents through an apoptotic mechanism. *Clin Cancer Res* 1997 Nov; 3(11):2017-24.
9. Gershenson DM, Silva EG, Levy L, Burke TW, **Wolf JK**, Tornos C. Ovarian serous borderline tumors with invasive peritoneal implants. *Cancer* 1998 Mar; 82(6)(6):1096-103.
10. Brader KR, **Wolf JK**, Chakrabarty S, Price JE. Epidermal growth factor receptor (EGFR) antisense transfection reduces the expression of EGFR and suppresses the malignant phenotype of a human ovarian cancer cell line. *Oncol Rep* 1998 Sep-Oct; 5(5):1269-74.
11. Price JE, **Wolf JK**, Pathak S. Distinctive karyotypes and growth patterns in nude mice reveal cross-contamination in an established human cancer cell line. *Oncol Rep* 1998 Jan-Feb; 5(1)(1):261-6.
12. **Wolf JK**, Kim TE, Fightmaster D, Bodurka D, Gershenson DM, Mills G, Wharton JT. Growth suppression of human ovarian cancer cell lines by the introduction of a p16 gene via a recombinant adenovirus. *Gynecol Oncol* 1999 Apr; 73(1)(1):27-34.
13. **Wolf JK**, Mullen J, Eifel PJ, Burke TW, Levenback C, Gershenson DM. Radiation treatment of advanced or recurrent granulosa cell tumor of the ovary. *Gynecol Oncol* 1999 Apr; 73(1):35-41.
14. **Wolf JK**, Mills GB, Bazzet L, Bast RC, Roth JA, Gershenson DM. Adenovirus-mediated p53 growth inhibition of ovarian cancer cells is independent of endogenous p53 status. *Gynecol Oncol* 1999 Nov; 75(2)(2):261-6.
15. Gershenson DM, Morris M, Burke TW, Levenback C, **Wolf JK**, Lee JJ, Thall PF, Atkinson EN, Silva EG, Wharton JT. A phase I trial of intravenous melphalan, paclitaxel, and cisplatin plus granulocyte-colony stimulating factor in patients with suboptimal advanced epithelial ovarian carcinoma or peritoneal carcinoma. *Cancer* 1999 Dec;86(11):2291-300.
16. Bodurka-Bevers, Basen-Engquist KM, Fitzgerald MA, Bevers MW, **Wolf JK**, Levenback C, Gershenson DM. Depression may worsen quality of life in patients with epithelial ovarian cancer. *Gynecol Oncol* 1999;72:449.
17. Bodurka-Bevers D, Basen-Engquist K, Carmack CL, Fitzgerald MA, **Wolf JK**, de Moor C, Gershenson DM. Depression, anxiety, and quality of life in patients with epithelial ovarian cancer. *Gynecol Oncol* 2000 Sep; 78(3)(3 Pt 1):302-8.
18. Parker LP, **Wolf JK**, Price JE. Adenoviral-mediated gene therapy with Ad5CMVp53 and Ad5CMVp21 in combination with standard therapies in human breast cancer cell lines. *Ann Clin Lab Sci* 2000 Oct; 30(4)(4):395-405.
19. Gordinier ME, Ramondetta LM, Parker LP, **Wolf JK**, Follen M, Gershenson DM, Bodurka-Bevers D. Survey of female gynecologic oncologists and fellows: balancing professional and personal life. *Gynecol Oncol* 2000 Nov; 79(2)(2):309-14.
20. Ramondetta L, Mills GB, Burke TW, **Wolf JK**. Adenovirus-mediated expression of p53 or p21 in a papillary serous endometrial carcinoma cell line (SPEC-2) results in both growth inhibition and apoptotic cell death: potential application of gene therapy to endometrial cancer. *Clin Cancer Res* 2000 Jan; 6(1)(1):278-84.
21. Donato, Gershenson D, Ippoliti C, Wharton JT, Bast Jr RC, Aleman A, Anderlini P, Gajewski JG, Giralt S, Molidrem J, Ueno N, Lauppe J, Korbling M, Boyer J, Bodurka-Bevers D, Bevers M, Burke T, Freedman R, Levenback C, **Wolf JK**, Champlin RE. High-dose ifosfamide and etoposide with filgrastim for stem cell mobilization in patients with advanced ovarian cancer. *Bone Marrow Transplant* 2000; 25(11):1137-1140.
22. Verschraegen, Levenback C, Vincent M, **Wolf JK**, Bevers M, Loyer E, Kudelka AP, Kavanagh JJ. Phase II study of intravenous DX-8951f in patients with advanced ovarian, tubal, or peritoneal cancer refractory to platinum, taxane, and topotecan. *Annals NY Acad Sci* 2000;922:349-51.
23. Munkarah A, Levenback C, **Wolf JK**, Bodurka-Bevers D, Tortolero-Luna G, Morris RT, Gershenson DM. Secondary cytoreductive surgery for localized intra-abdominal recurrences in epithelial ovarian cancer. *Gynecol Oncol* 2001 May; 81(2):237-41.
24. Modesitt SC, Ramirez P, Zu Z, Bodurka-Bevers D, Gershenson D, **Wolf JK**. In vitro and in vivo adenovirus-mediated p53 and p16 tumor suppressor therapy in ovarian cancer. *Clin Cancer Res* 2001 Jun; 7(6):1765-72.
25. Hortobagyi GN, Ueno NT, Xia W, Zhang S, **Wolf JK**, Putnam JB, Weiden PL, Willey JS, Carey M, Branham DL, Payne JY, Tucker SD, Bartholomeusz C, Kilbourn RG, De Jager RL, Sneige N, Katz RL, Anklesaria P, Ibrahim NK, Murray JL, Theriault RL, Valero V, Gershenson DM, Bevers MW, Huang L, Lopez-Berestein G, Hung MC. Cationic liposome-mediated E1A gene transfer to human breast and ovarian cancer cells and its biologic effects: a phase I clinical trial. *J Clin Oncol* 2001 Jul 15;19(14):3422-33.
26. Ramirez PT, Levenback C, Burke TW, Eifel P, **Wolf JK**, Gershenson DM. Sigmoid perforation following radiation therapy in patients with cervical cancer. *Gynecol Oncol* 2001 Jul;82(1):150-5.
27. Donato ML, Gershenson DM, Wharton JT, Ippoliti CM, Aleman AS, Bodurka-Bevers D, Bevers MW, Burke TW, Levenback CF, **Wolf JK**, Freedman RS, Bast RC, Gajewski JL, Champlin RE. High-dose topotecan, melphalan, and cyclophosphamide (TMC) with stem cell support: a new regimen for the treatment of advanced ovarian cancer. *Gynecol Oncol* 2001 Sep;82(3)(3):420-6.

28. Robinson JB, Singh D, Bodurka-Bevers DC, Wharton JT, Gershenson DM, **Wolf JK**. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gynecol Oncol* 2001 Sep; 82(3):550-8.
29. Levenback C, Coleman RL, Burke TW, Bodurka-Bevers D, **Wolf JK**, Gershenson DM. Intraoperative lymphatic mapping and sentinel node identification with blue dye in patients with vulvar cancer. *Gynecol Oncol* 2001 Nov;83(2)(2):276-81.
30. Ramirez PT, Gershenson DM, Tortolero-Luna G, Ramondetta LM, Fightmaster D, Wharton JT, **Wolf JK**. Expression of cell-cycle mediators in ovarian cancer cells after transfection with p16(INK4a), p21(WAF1/Cip-1), and p53. *Gynecol Oncol* 2001 Dec; 83(3)(3):543-8.
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Invited Articles

1. **Wolf JK**, Wharton JT. Wild-type p53 overexpression: what role in tumorigenesis? *Gynecol Oncol* 60(3):337-8, 3/1996.
2. **Wolf JK**. Management of wound complications. *Clin Consults in Ob/Gyn* 8:79-84, 1996.
3. **Wolf JK**, Ramirez PT. The molecular biology of cervical cancer. *Cancer Invest* 19(6):621-9, 2001.
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11. **Wolf JK**, Slomovitz BM. Novel biologic therapies for the treatment of endometrial cancer. *Int J Gynecol Cancer* 15(2):411, 2005.
12. **Wolf JK**. Prevention and treatment of vaginal stenosis resulting from pelvic radiation therapy. *Community Oncol* 3(10):665-71, 2006.

Editorials

1. **Wolf JK**, Wharton JT. Wild-type p53 overexpression: what role in tumorigenesis? *Gynecol Oncol* 60(3):337-8, 1996.

Other Articles

1. **Wolf JK**. Gynecologic Cancer Treatment Update (Highlights from ASCO 2003). *Vital Signs Monograph*, Fall, 2003.
2. Herzog, Coleman R, McGuire, Monk B, Spriggs D, **Wolf JK**. Patterns of Practice in Selected Gynecologic Malignancies. Colloquium at the Annual Meeting on Women's Cancer 2005 36th Annual Meeting of the Society of Gynecologic Oncologist . (SGO Monograph), 2005.

Abstracts (Past 5 years)

1. Jhingran A, Ramondetta L, Bodurka D, Brown J, Eifel P, Garcia M, Lu K, **Wolf JK**, Burke T. A prospective phase II study of chemoradiation followed by adjuvant chemotherapy for stage I-IIIa uterine papillary serous carcinoma. *Gynecologic Oncology* 116(3, S1):S9 (#15), 3/2010.
2. Brown J, Sood A, Ramirez P, Ramondetta L, Coleman R, Levenback C, Jung M, **Wolf JK**. Combination gemcitabine and cisplatin are highly active in endometrial carcinoma: Results of a prospective phase II trial. *Gynecologic Oncology* 116(3, S1) (#49), 3/2010.
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8. Meyer LA, Slomovitz BM, Djordjevic B, Munsell M, Broaddus R, Iglesias DA, Westin SN, Gershenson DM, **Wolf JK**, Lu KH. Can negative biomarkers be helpful? A novel combination test to predict non-response to inhibition of the mammalian target of rapamycin (mTOR) pathway in endometrial cancer. *Society of Gynecologic Oncologists*, 3/2012
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Book Chapters

1. Hallum AV, III, Coleman RL, **Wolf JK**. Gynecologic Oncology. In: The M. D. Anderson Surgical Oncology Handbook. Ed(s) David H. Berger, Barry W. Feig, and George M. Fuhrman. Little Brown and Company: Boston, MA, 326-368, 1995.
2. Bevers MW, Bodurka Bevers DC, **Wolf JK**. Gynecologic Cancers. In: The M. D. Anderson Surgical Oncology Handbook, Second Edition. Ed(s) Barry W. Feig, David H Berger, and George M. Fuhrman. Lippincott Williams & Wilkins: Philadelphia, 377-424, 1998.

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Letters to the Editor

N/A

Manuals, Teaching Aids, Other Teaching Publications

N/A

Other Publications

N/A

EDITORIAL AND REVIEW ACTIVITIES

Editor/Service on Editorial Board(s)

N/A

Member of Editorial Review Board

Editorial Board Member, Clinical Ovarian Cancer: & Other Gynecologic Malignancies, CIG Media, 2008-present

Editorial Board Reviewer, European Journal of Clinical and Medical Oncology, San Lucas Medical Limited c/o Barefoot Investment Ltd, Editorial Board of the Peer Reviewed Journal, 2010-present

Editorial Board Reviewer, American Society of Clinical Oncology, 2013 ASCO Educational Book

Editorial Advisory Board Reviewer, ADC Review/Journal of Antibody-drug Conjugates, 2013

Journal Reviewer

Reviewer, Gynecologic Oncology, 1995-present

Adhoc Reviewer, Obstetrics and Gynecology, 1996-present

Adhoc Reviewer, Clinical Cancer Research, 1998-present

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Adhoc Reviewer, Journal of Clinical Oncology, 1999-present

Adhoc Reviewer, American Journal of Pathology, 2001-present

Adhoc Reviewer, American Journal of Obstetrics and Gynecology, 2005-present

Other Editorial and Review Activities

Editor, Help Break the Silence. Talk about Ovarian Cancer, National Ovarian Cancer Coalition - NOCC Editors Event; New York, NY, April 29, 2008

TEACHING

Teaching Within Current Institution – Banner MD Anderson Cancer Center

Formal Teaching

Courses Taught

N/A

Training Programs

N/A

Other Formal Teaching

Lecturer, 1995-1999, Gynecologic Oncology for Enterostomal Therapy Nurses / Role of Gynecologic Oncologist talk given twice a year
1995-1999

Lecturer, 1998, Advances in Research for Ovarian Cancer / Sprint for Life Symposium
1998

Lecturer, 1998, Ovarian Cancer Treatment: Molecular Approaches / Grand Rounds
1998

Lecturer, 1999, Advances and Innovations in Ovarian Cancer / Sprint for Life Symposium

1999

Supervisory Teaching

Committees

Advisory Committees

Thesis Advisory Committee, GSBS, Christine Lee, MD, 2001–2003

Thesis Advisory Committee, GSBS, David Crotzer, MD, 2002–2004

Thesis Advisory Committee, GSBS, Monique Nillson, 2003–2005

Supervisory Committees

Chair, Thesis Supervisory Committee, GSBS, David Crotzer, MD, 2002–2004

Examining Committees

N/A

Direct Supervision

Undergraduate and Allied Health Students

N/A

Medical Students

4th Year Medical Students- Midwestern University, Phoenix, AZ

Graduate Students

GSBS, David Crotzer, MD, 2002–2004

Postdoctoral Research Fellows

Tae-Eu Kim Koreai, 1996–1997

Basic Science, Lois Ramondetta, MD, 1998

Basic Science, Pedro Ramirez, MD, 1998

Basic Science, Susan Modesitt, MD, 1999

Basic Science, Veronica Schimp, DO, 2000

Basic Science, Janos Tanyi, 2001–2004

Basic Science, Dwayne Jenkins, MD, 2001

Basic Science, David Crotzer, MD, 2002–2004

Clinical Residents and Fellows

Diljeet Singh, 7/1996–6/1999

Kenny Bozorgi, 7/1996–6/1999

Terri Pustilnik, 7/1996–6/1999

Lois M. Ramondetta, 7/1997–6/2000

Lynn P. Parker, 7/1997–6/2000

Mary E. Gordinier, 7/1997–6/2000

Carlos Herrera, 7/1998–6/2001

Lloyd West, 7/1998–6/2001

Pedro T. Ramirez, 7/1998–6/2001

Jubilee Brown Robinson, 7/1999–6/2002

Matthew Anderson, 7/1999–6/2002

Susan Modesitt, 7/1999–6/2002

Hyun Shvartsman, 7/2000–6/2003

Sean Tedjerati, 7/2000–6/2003

Veronica Schimp, 7/2000–6/2003

Alfred Dwayne Jenkins, 7/2001–6/2004

Amir Jazaeri, 7/2001–6/2004

Jonathan Oh, 7/2001–6/2004

Christine Lee, 7/2001–6/2005

Michael Frumovitz, 7/2001–6/2005

Sachin Apte, 7/2001–6/2005

Brian Slomovitz, 7/2002–6/2006

David Crotzer, 7/2002–6/2006

Premal Thaker, 7/2002–6/2006

Salvador Saldivar, 7/2003–6/2006

Charles Landen, 7/2003–6/2007

Pamela Soliman, 7/2003–6/2007

Aparna Kamat, 7/2004–6/2008

Kathleen Schmeler, 7/2004–6/2008

Liz Han, 7/2004–6/2008

Michael Milam, 7/2005–6/2009

William Merritt, 7/2005–6/2009

Yvonne Lin, 7/2005–6/2009

John Moroney, 7/2006–6/2010

Robin Lacour, 7/2006–6/2010

Shannon Westin, 7/2006–6/2010

Whitney Spannuth, 7/2006–6/2010

Alpa Nick, 7/2007–6/2011

Celestine Tung, 7/2007–6/2011

Larissa Meyer, 7/2007–6/2011

Jennifer Kelly Burzawa, 7/2008–6/2012

Matthew Peter Schlumbrecht, 7/2008–6/2012

Rebecca Lynn Stone, 7/2008–6/2012

Other Supervisory Teaching

Julie Huh, 4th year medical student, Graduate Students, 1996

Lisa Bazzett, Clinical Residents and Fellows, 1997

Mentor, Global Academic Programs - University Hospital Juan Canalejo, Spain, Ovidio Fernandez-Calvo, MD, Foreign Visitor, 2/2009-5/2009

Mentor, Sister Institution Associates - Fudan Cancer Hospital, China, Global Academic Programs, Jie Tang, MD, Foreign Visitor, 6/2009-12/2009

Teaching Outside of Current Institution

Formal Teaching

Courses Taught

Current Directions in Cancer Therapy & Research, National Ovarian Cancer Coalition

Yearly, 1998-present

A-Z Gene Therapy Replacing p53 to achieve antitumor effect, Society of Gynecologic Oncologists

Lecturer, Gene Therapy for Gynecologic Malignancies, University of Texas Medical School

Training Programs

N/A

Other Formal Teaching

N/A

Supervisory Teaching

Committees

Advisory Committees

N/A

Supervisory Committees

PhD Committee, Lee Seabrooke, Arizona State University, Tempe, AZ

Examining Committees

N/A

Direct Supervision

Undergraduate and Allied Health Students

N/A

Medical Students

N/A

Graduate Students

N/A

Postdoctoral Research Fellows

N/A

Clinical Residents and Fellows

N/A

Other Supervisory Teaching

N/A

CONFERENCES AND SYMPOSIA

Organization of Conferences/Symposia (Include chairing session)

N/A

Presentations at National or International Conferences

Invited

Characterization of two populations of the human ovarian cancer cell line, 2774, that express different levels of epidermal growth factor receptor, AACR Annual Meeting, 1993

Characterization of two populations of the human ovarian cancer cell line, 2774, that express different levels of epidermal growth factor receptor, Felix Rutledge Society Annual Meeting, 1993

Enhanced c-erbB-2/neu expression in human ovarian cancer cells correlates with more severe malignancy that can be suppressed by E1A, American Radium Society Annual Meeting, Aruba, 1993

Relationship between expression of c-erbB-2/neu and the malignant phenotype of a human ovarian cancer cell line (SKOV3), Felix Rutledge Society Annual Meeting, 1993

Expression of adenovirus β -galactosidase in rhesus monkey cervix and growth inhibition of human cervical cancer cells by recombinant p53, Felix Rutledge Society Annual Meeting, 1995

Growth inhibition of human ovarian cancer cells by the recombinant adenovirus-mediated transfer of a wild-type p53 gene, Society of Gynecologic Oncologists 26th Annual Meeting, San Francisco, CA, 1995

The significance of cone biopsy margins in patients with adenocarcinoma in situ of the cervix, Felix Rutledge Society Annual Meeting, 1995

A-Z Gene Therapy - Replacing p53 to achieve antitumor effect, Society of Gynecologic Oncologist, 1997

Growth inhibition of human ovarian cancer cells by combination treatment with cisplatin and transfection with adenovirus-mediated p53, Society of Gynecologic Oncologists 28th Annual Meeting, Phoenix, AZ, 1997

Replacing p53 to Achieve an Antitumor Effect, Society of Gynecologic Oncologist 28th Annual Meeting, Phoenix, AZ, 1997

Growth suppression of human ovarian cancer cell lines by the introduction of a P16 via a recombinant adenovirus, Society of Gynecologic Oncologists Annual Meeting, 1998

Cirugia Citorreductora VS Cirugia Minimay uimioterapia Adyuvante, Sociedad Venezolana De Oncologia, VIII Congreso Venezolano De Oncologia, Puerto La Cruz, Venezuela, 10/9/1998

Ganglio Centinela En El Manejo Del Cancer Vulva, Sociedad Venezolana De Oncologia, VIII Congreso Venezolano De Oncologia, Puerto La Cruz, Venezuela, 10/9/1998

Principios De Terapia Genetica Aplicados A Oncologia Media, Sociedad Venezolana De Oncologia, VIII Congreso Venezolano De Oncologia, Puerto La Cruz, Venezuela, 10/9/1998

Terapia Genetica En Cancer, Sociedad Venezolana De Oncologia, VIII Congreso Venezolano De Oncologia, Puerto La Cruz, Venezuela, 10/9/1998

Gene Therapy for Gynecologic Malignancies, Department of Gynecology Grand Rounds, University of Texas Medical School, Houston, TX, 9/28/1999

A phase I trial of ADP53 for ovarian cancer patients: Correlation with p53 and anti-adenovirus AB status, Society of Gynecologic Oncologist Annual Meeting, 2000

A Phase I Trial of Adp53 for Patients with Platinum- and Paclitaxel-Resistant Epithelial Ovarian Cancer, 31st Annual Meeting of the Society of Gynecologic Oncologists, San Diego, CA, 2/9/2000

Prognostic Factors in Endometrial Cancer, Society of Gynecologic Oncologists 2000 Winter Meeting, Park City, UT, 3/18/2000

Effect of Transfecting P16 & P53 Suppressors on Cell Growth and Apoptosis in Ovarian Cancer Cell Lines, American Association for Cancer Research, 91st Annual Meeting, San Francisco, CA, 4/1/2000

Womens Professional Development, Association of American Medical Colleges Professional Development Seminar for Junior Women Faculty, Association of American Medical Colleges, Reston, VA, 4/1/2000

A Phase I Trial of Adp53 (RPR/INGN 201) for Ovarian Cancer Patients: Correlation with P53 and Anti-Adenovirus Antibody Status, American Society of Clinical Oncology, New Orleans, LA, 5/22/2000

Gene Therapy in Patients with Epithelial Ovarian Cancer, Gynecologic Oncology Group, 7/2000

Application of Molecular Biology in Gynecologic Cancer, Annual Meeting of the Thai Gynecologic Oncology Group, Nakorn Nayok, Thailand, 8/12/2000

The Role of Liposomal Doxorubicin (Caelyx) in Ovarian Cancer, Annual Meeting of the Thai Gynecologic Oncology Group, Nakorn Nayok, Thailand, 8/12/2000

Gene Therapy for Cervical Cancer - An Update, 2nd Annual International Conference on Cervical Cancer, Houston, TX, 4/13/2002

In Vivo Adenovirus-Mediated p16 Tumor Suppressor Gene Therapy in Ovarian Cancer, Texas Forum on Female Reproduction 8th Annual Meeting, Houston, TX, 5/2/2002

A Phase II Study of Xeloda in Patients with Chemotherapy Resistant Recurrent Ovarian Cancer, ASCO 2002 Annual Meeting, Orlando, FL, 5/19/2002

The Role of Docetaxel in Gynecologic Malignancies, 40th Japanese Society of Clinical Oncology Annual Meeting, Juntendo University, Tokyo, Japan, 10/16/2002

Management of Ovarian cancer in the 21st Century-Surgery, Chemotherapy, and Molecular Therapy, 40th Japanese Society of Clinical Oncology Annual Meeting, Jutendo University, Tokyo, Japan, 10/17/2002

Surgical Management of Gynecologic Malignancies, 40th Japanese Society of Clinical Oncology Annual Meeting, Jutendo University, Tokyo, Japan, 10/17/2002

A Phase I/II Study to Evaluate the Optimum Biologic Dose of PEG-Intron in Patients with Platinum-Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer, 11th SPORE Investigators Workshop, Baltimore, WA, 7/8/2003

A Phase I/II Study to Evaluate the Optimum Biologic Dose of PEG-Intron in Patients with Platinum-Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer, 11th SPORE Investigator's Workshop, Baltimore, MD, 7/9/2003

P53 Targeted Therapy, 4th International Ovarian Cancer Conference, MSKCC, New York, NY, 9/11/2003

mTOR inhibition is a rational target for the treatment of endometrial cancer, ASCO 40th Annual Meeting, New Orleans, LA, 6/5/2004

Cervical and Endometrial Cancers - Preferred Treatment and Management Options, CME Conference, Hoag Cancer Center, Huntington Beach, CA, 1/28/2005

Health issues and risk factors for Breast and Gynecologic Cancers, Hadassah Check it Out program, San Antonio, TX, 2/9/2005

Cervical Cancer, Ovarian Cancer:What We Need to Know, Women's Health On Alert, Wellesley College, Wellesley, MA, 4/2/2005

Wiley, Miryam (Townsmen Correspondent) Women and hormonal health the expert views., The Wellesley Townsman: townonline.com, Wellesley College, Wellesley, MA, 4/7/2005

Transitioning from Fellow to Faculty: How to go About Setting up an Independent Laboratory, and How to be a Mentor for Students, Residents and Fellows, 2005 Southern Regional Professional Development Conference - Successful Strategies for Women in Academic Medicine, Little Rock, AR, 4/16/2005

The Role of COUP-TFII in Ovarian Cancer, Grand Rounds, Baylor College of Medicine, Houston, TX, 5/6/2005

Biologic Therapies Should be Used as Single Agents in Ovarian Cancer Clinical Trials, Felix Rutledge Society 36th Annual Meeting, Mackinac Island, MI, 7/15/2005

Surgical Treatment of Ovarian Cancer Indications and Advances in the 21st Century, Chinese Society of Gynecologic Oncology, Tsinghua University, Nanjing, China, 6/3/2006

Surgical Treatment of Ovarian Cancer Indications and Advances in the 21st Century and Beyond, International Forum on the Mechanisms and Management of Ovarian Cancer, Peking University People's Hospital, Beijing, China, 6/9/2006

Thymidine Kinase Inhibitors in Gynecologic Malignancies, Felix Rutledge Society 36th Annual Meeting, Berlin, Germany, 9/7/2006

Intraperitoneal Chemotherapy for Optimally Debulked Ovarian Cancer and Emerging Therapies in Ovarian Cancer, 6th Samsung Medical Center - M. D. Anderson Cancer Center International Symposium, Seoul, Korea, Republic of, 11/4/2006

Ovarian Carcinoma for the General Oncologist, Third Symposium, Pursuit of Excellence: Addressing Issues and Trend in Oncology Nursing, UT M D Andersons Physicians Network, Santa Barbara, CA, 7/13/2007

Early Detection and Treatment of Ovarian Cancer, SGO, Tampa, FL, 3/9/2008

Optimizing Treatment Choices in Ovarian Cancer, SGO, Tampa, FL, 3/9/2008

Advances in the Management of Ovarian Stromal Tumors, ASCO, Chicago, IL, 5/31/2008

Ovarian Cancer, Uterine Cancer, Cervical Cancer, Hospital Israelita Albert Einstein and M D Anderson Cancer Center, Hospital Israelita Albert Einstein and M D Anderson Cancer Center, Sao Paulo, Brazil, 6/17/2008

Minimally Invasive Surgery in Gynecology Oncology, II International Symposium of Gynecology Oncology - Hospital Sirio-Libanes, Sao Palo, Brazil, 11/7/2008

Gene Therapy and Targeted Therapies in Gynecologic malignancies, II International Symposium of

Gynecology Oncology - Hospital Sirio-Libanês, São Paulo, Brazil, 11/8/2008
Gynecologic Cancers. What you need to know about Ovarian, Uterine, and Cervix Cancers, Albert Einstein Instituto Israelita De Ensino E Pesquisa, São Paulo, Brazil, 6/23/2009
Course Director, 8th International Conference on Ovarian Cancer, Memorial Sloan-Kettering Cancer Center, New York, NY, 9/24/2009
Treatment of Ovarian Cancer 21st Century and Beyond, 6th Chinese Conference on Oncology and the 9th Cross-Strait Conference on Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, 5/21/2010

Chemotherapy Session Moderator, The 9th International Conference on Ovarian Cancer, Houston, TX
12/2/2011

Scientific Exhibitions

Current Directions in Cancer Therapy & Research, Cancer in Women: A Comprehensive Scientific Symposium on the Gynecologic Malignancies, National Ovarian Cancer Coalition, San Diego, CA, 2/4/2000
The Role of Gemcitabine in Ovarian Cancer, Lilly Oncology Advisory Meeting, Indianapolis, IN, 2/28/2002
Current and New Treatment Strategies for Ovarian Cancer, Grand Rounds, University of Medicine & Dentistry of New Jersey, Newark, NJ, 3/27/2002
Challenging Cases in Gynecologic Oncology, Network for Oncology Communication & Research, Las Vegas, NV, 8/17/2002
Cancer in Women: A scientific update in prevention, screening, treatment and risk management for ovarian and cervical malignancies, National Ovarian Cancer Coalition, Inc., Boston, MA, 10/10/2002
Ethical Dilemmas in Clinical Trials, John J. Molitor Lectureship CME Conference, University of California, Irvine, CA, 10/30/2002
The Application of Gene Therapy for Gynecologic Malignancies, Texas Medical Center Gene Therapy Symposium, Houston, TX, 11/11/2002
Indication for and Value of Screening for Ovarian Cancer, CME Conference, Inova Institute of Research & Education, Fairfax, VA, 11/15/2002
Treatment of recurrent Ovarian Cancer, Grand Rounds, Walter Reed Army Medical Center, Bethesda, MD, 12/4/2002
Current Treatment Strategies for Gynecologic Cancers, SGO Symposium 34th Annual Meeting, New Orleans, LA, 2/2/2003
Panel Physician - Ovarian Cancer Panel, The National Comprehensive Cancer Network on Ovarian Cancer Panel, Chicago, IL, 2/7/2003
Novel Therapeutics for Endometrial Cancer, 2003 SGO Winter Meeting, Breckenridge, CO, 3/7/2003
Novel Approaches to the Treatment of Gynecological Cancer, 2003 Oncology Forum, Fox Chase Cancer Center, Philadelphia, PA, 4/26/2003
Satellite Broadcast, Highlights from ASCO 2003, American Academy of the CME, Inc., Newark, NJ, 6/18/2003
What's New in Ovarian Cancer Treatment, NOCC National Conference, Ft. Lauderdale, FL, 11/8/2003
Ovarian Cancer: A Progress Report, 4th Annual Primary Care and Prevention conference, Atlanta, GA, 10/25/2004
Current & New Treatments for Ovarian Cancer, NOCC Conference, Philadelphia, PA, 10/30/2004
Clinical Trials, NOCC National Meeting, Ft. Lauderdale, FL, 11/13/2004
Cancer In Women: a Scientific Update on Ovarian Cancer-Prevention, Screening and Treatment, CME Conference, CME Massachusetts Medical Society & NOCC, 2/4/2005
Phase II Trials among the Ovarian SPORE Programs, Ovarian State of the Science Meeting - GOG Retreat, Bethesda, MD, 9/15/2005
Challenging Cases in Women's Health Recurrent Ovarian Cancer at 8 Months, NMCR Challenging Cases in Gyn Oncology and Breast Cancer, Miami, FL, 6/17/2006
How to Survive and Thrive as a Female Physician in Gynecologic Oncology, Japanese Society of Gynecologic Oncology 42nd Annual Meeting, Tokyo, Japan, 6/28/2007
What's New Gynecologic Oncology? An Update on Translational and Clinical Research, Japanese Society of Gynecologic Oncology 42nd Annual Meeting, Tokyo, Japan, 7/2/2007
Ovarian Carcinoma for the General Oncologist, UT M D Anderson Cancer Center and M D Anderson Physicians Network 3rd Annual Symposium
The University of Texas MD Anderson Cancer Center, Santa Barbara, CA, 7/9/2007
Ovarian Expert Recap - Clinical Options, ASCO, Chicago, IL, 5/30/2008
Controversial Issues in Recurrent Ovarian Cancer, Felix

Rutledge Society Meeting, Buenos Aires, Argentina, 4/29/2009

Conversations with Oncology Investigators, Bridging the Gap between Research and Patient Care,
Research to Practice CME Program, 01/2013

National Seminar Invitations

Attended, Association of American Medical Colleges Professional Development Seminar for Junior
Women Faculty, Reston, Virginia, April 1-4, 2000

Gynecologic Cancers 2003 Treatment Update, CHRISTUS Spohn Shoreline Tumor Conference-CME,
CHRISTUS Spohn Shoreline, Corpus Christi, TX, 8/27/2003

Update in the Management of Ovarian Cancer, Symposium on Women's Cancer, The Cleo Craig
Memorial Cancer and Research Clinic, Lawton, OK, 8/28/2004

Palliative Care Issues for Patients Facing Advanced Ovarian Cancer, MDACC Physicians Network,
Christus Schumpert Cancer CME Symposium, MDACC Physicians Network, Christus Schumpert Cancer
CME Symposium, Shreveport, LA, 10/22/2004

PV, The Abnormal Pap Smear, and Cervical Cancer, MDACC Physicians Network, Christus Schumpert
Cancer CME Symposium, MDACC Physicians Network, Christus Schumpert Cancer CME Symposium,
Shreveport, LA, 10/22/2004

Metastatic Cervical Cancer, Cancer 2005: Preferred Treatment and Management Options, Hoag Cancer
Center CME Oncology Meeting, Huntington Beach, CA, 1/28/2005

Recurrent Endometrial Cancer, Cancer 2005: Preferred Treatment and Management Options, Hoag
Cancer Center CME Oncology Meeting, Huntington Beach, CA, 1/28/2005

Clinical Trials - Understanding, Navigating & Accessing Clinical Trials, Georgia Ovarian Cancer
Awareness Conference, Georgia Ovarian Cancer Awareness Conference, Atlanta, GA, 2/19/2005

Cervical Cancer, Ovarian Cancer: What We Need to Know, Women's Health on Alert, Wellesley College,
Wellesley, MA, 4/2/2005

Recurrent Endometrial Cancer Case#5, Challenging Cases in Women's Health, NOCR, Las Vegas, NV,
8/6/2005

Breaking Sound Barriers: Cutting Edge Research from the Lab and Clinical Trials, Turn the Volume Up-
Ovarian Cancer National Alliance Conference, NOCC, Atlanta, GA, 9/29/2005

Clinical Trials 101, Turn the Volume Up-Ovarian Cancer National Alliance Conference, NOCC, Atlanta,
GA, 9/29/2005

Risk Factors and Genetic Risk factors Regarding Ovarian Cancer, Diagnosis and Treatment of Ovarian
Cancer - Beyond Chemotherapy National Ovarian Cancer Coalition Symposium, NOCC, Philadelphia,
PA, 10/29/2005

Clinical Trials, National Ovarian Cancer Coalition Mini-Conferences, NOCC, Silver Springs, MD,
11/12/2005

Current & New Treatments for Ovarian Cancer, Grand Rounds, Advocate Christ Medical Center, Oak
Lawn, IL, 1/12/2006

Progress and Treatment for Ovarian Cancer, Grand Rounds CME, MacNeal Hospital, Berwyn, IL,
4/25/2006

Women and Cancer: A Focus on Cervical and Ovarian Cancer, Oncology Nursing and Pharmacy
Conference Series 2006: Collaboration for Advancing the Quality of Community Cancer Care, UTMB
Office of Continuing Education, San Diego, CA, 11/18/2006

Women and Cancer: A Focus on Cervical and Ovarian Cancer, Oncology Nursing and Pharmacy
Conference Series 2006: Collaboration for Advancing the Quality of Community Cancer Care, UTMB
Office of Continuing Education, Williamsburg, VA, 12/2/2006

Future Directions and New Frontiers in Individualized Therapeutic Approaches, SGO-CME Certified
Satellite Symposium Management of Recurrent Epithelial Ovarian Cancer: Current Standards and Novel
Approaches, Society of Gynecologic Oncologist, San Diego, CA, 3/5/2007

Treatment of a Patient with Recurrent, Platinum-Resistant Disease, SGO-CME Certified Satellite
Symposium Management of Recurrent Epithelial Ovarian Cancer: Current Standards and Novel
Approaches, Society of Gynecologic Oncologist, San Diego, CA, 3/5/2007

Northwestern Prentice Women's Hospital, Guest Speaker, Chicago, IL. 02/08/2008 "From Bench to
Bedside - My Personal Experience

Texas Medical Association, Ovarian Cancer Advisory Panel Meeting, Austin, TX, July 21, 2008

EIF Callaway Golf Foundation Women's Cancer Initiative Annual Meeting, "Ovarian Cancer Research
Program", Carlsbad, CA, August 8, 2008

The Impact of Stress, Gynecologic Cancer Foundation, NYU Langone Medical Center, New York, NY,
11/1/2008

Global Academic Programs (formerly Sister Institution Conference MDACC), Chair the Working Group on
Gynecologic Malignancies, Houston, TX, 6/6/2008

M D Anderson Cancer Center Development Symposium, accompanied Dr. Mendelsohn and spoke at the

Southern Hills Country Club, Tulsa, OK, June 24, 2008

Gastrointestinal Cancer Retreat and PI3K Workshop: CCSG Programs Onstead Auditorium, BSRB Mitchell Building

Advisor, Entereg Complex Gynecologic Surgery Advisory Meeting, GSK, Philadelphia, PA, December 5-6, 2008

Texas Medical Association, Ovarian Cancer Advisory Panel Meeting, Austin, TX, January 9, 2009

Advisor, Yondelis Advisory Board Meeting, Centocor Ortho Biotech, Newport Beach, CA, February 20-21, 2009

Texas Medical Association, Ovarian Cancer Advisory Panel Meeting, Austin, TX, July 14, 2009

Career Pathways for Women in Science and Medicine & What the Careers of the Future Will Hold and More, Dinner with the Experts, Spring Branch Independent School District, Houston, TX, January 21, 2010

Faculty, CE-Continuing Education Program, OncoBeat ASCO 2010: Reporting the News. Beating Cancer. Educational Concepts Group, LLC; Chicago, IL; June 7, 2010.

Advanced Ovarian Cancer, Facilitator for Interactive Case Discussions, SGO, March 26, 2012

Guest Speaker, "The Ethics of Clinical Trials", Phoenix Chapter of Association of Clinical Research Professionals, July 2013

Lectureships/Visiting Professorships

Gynecologic Oncology Overview, Grand Rounds, Beaumont Hospital, Beaumont, TX, 4/17/1997

Abnormal Uterine Bleeding & Endometrial Cancer, Grand Rounds, St. Frances Cabrini Hospital, Alexandria, LA, 8/24/1999

Gynecologic Oncology Overview, Grand Rounds, Nacogdoches/San Augustine Medical Society, Nacogdoches, TX, 11/10/1999

Gene Therapy for Gynecologic Malignancies, University of Minnesota Fellowship Program, Minneapolis, MN, 12/14/1999

Gynecologic Cancers: Diagnosis, Treatment & Outcomes-Where We've Been & Where We're Going, Grand Rounds, Christus Spohn Health System Tumor Conference, Corpus Christi, TX, 9/20/2000

Current and New Treatment Strategies for Ovarian Cancer, CME, University of Medicine & Dentistry of New Jersey, Medical School, Newark, NJ, 3/27/2002

Ethical Dilemmas in Clinical Trials, John J. Molitor Lectureship, University of California, Irvine, CA, 10/30/2002

The Application of Gene Therapy for Gynecologic Malignancies, Texas Medical Center Gene Therapy Symposium, Texas Medical Center, Houston, TX, 11/11/2002

Indication for and Value of Screening for Ovarian Cancer, CME, Inova Institute of Research & Education, Fairfax, VA, 11/15/2002

Treatment of recurrent Ovarian Cancer, CME, Walter Reed Army Medical Center, Bethesda, MD, 12/4/2002

Novel Therapeutics for Endometrial Cancer, 2003 SGO Winter Meeting, Society of Gynecologic Oncologist, Breckenridge, CO, 3/7/2003

Physician Advisor for Gynecological Cancer Advisory Board, Novel Approaches to the Treatment of Gynecological Cancer, 2003 Oncology Forum, Fox Chase Cancer Center, Philadelphia, PA, 4/26/2003

Translational Research from Bench to Bedside One Gynecologic Oncologist's Experience, Bench to Bedside Symposium, NYU Medical Center, New York, NY, 5/20/2005

Progress and Treatment of Ovarian Cancer, MDACC Faculty Speakers Bureau, CME - OB/GYN Grand Rounds, St. David's Healthcare, Austin, TX, 10/18/2005

Progress and Treatment of Ovarian Cancer, MDACC Faculty Speakers Bureau, CME - University Hospital Grand Rounds, University Health Care System, Augusta, GA, 10/20/2005

Current and New Treatments for Ovarian Cancer, CME, Advocate Christ Hospital, Oak Lawn, IL, 1/12/2006

The Ethics of Clinical Trials, University of Minnesota Gynecologic Oncology Consensus Conference, University of Minnesota, Minneapolis, MN, 5/8/2006

Comprehensive Management of Ovarian Cancer: Current Treatment and Maximizing Quality of Life, CME-Medical Communications Media, Novato Community Hospital, Novato, CA, 5/7/2007

Comprehensive Management of Ovarian Cancer: Current Treatment and Maximizing Quality of Life, Grand Rounds-Medical Communications Media, University of Pittsburgh, Pittsburgh, PA, 6/5/2007

Treatment of Ovarian Cancer - 21st Century and Beyond, Grand Rounds, UC Davis Medical Center, Gynecologic Oncology, Sacramento, CA, 12/17/2008

Gynecologic Cancers: Uterine Cancer, CME: Update on Endometrial Cancer, Citizens Medical Center, Office of Continuing Medical Education, Victoria, TX, 1/11/2010

NATIONAL CONFERENCES- INVITED/ AND OR SPEAKER

Treatment of Ovarian Cancer, National Ovarian Cancer Coalition State Chapters Meeting, NOCC, Ft. Lauderdale, FL, 11/5/1999

Commencement speaker, East Liverpool High School, East Liverpool, OH, 6/1/2000

Gynecologic Cancers: Diagnosis, Treatment & Outcomes-Where We've Been & Where We're Going, 2nd Annual "Closing Gaps & Opening Doors Conference for Working Women, U.S. Department of Labor, Women's Bureau Region VI, Austin, TX, 10/5/2000

Talk-back Session - Moderator, Wet State Theater, Alley Theater, UT M D Anderson Cancer Center & the Stanford Foundation, Austin, TX, 5/31/2001

Interferon-g in the Management of Ovarian Cancer clinical Advisory Program, Advisory Program, InterMune Pharmaceuticals, Houston, TX, 6/21/2001

Current & New Treatments for Ovarian Cancer, Cancer in Women: A Scientific Update in Prevention, Screening and Treatment for Ovarian Cancer, NOCC, Houston, TX, 1/1/2004

Management of Gynecologic Cancer, Sanofi-Synthelabo Oncology Health Science Advisory Board Meeting, Sanofi-Synthelabo Oncology, Dallas, TX, 4/24/2004

Controversies in Ovarian Cancer, ACOG Update, Audiotaped Tele-Conference, ACOG, Houston, TX, 5/14/2004

Health issues and risk factors for Breast and Gynecologic Cancers, Hadassah Check it Out program to educate young women in Houston Independent School District, Worthing High School, Houston, TX, 2/9/2005

Screening for Gynecologic Cancers, CME Memorial Hermann Southwest Hospital, Memorial Hermann Southwest Hospital, Houston, TX, 3/8/2005

The Role of COUP-TFII in Ovarian Cancer, Arthur M. Faris, Sr., MD Resident Research Day, Baylor College of Medicine, Obstetrics and Gynecology, Houston, TX, 5/6/2005

Menopause The Musical Out Loud - Breaking the Silence on Ovarian Cancer, National Ovarian Cancer Coalition, Matrix Graphix, and Ovarian Cancer National Alliance Aging Out Loud Tour, TOC Productions Inc., www.menopausethemusical.com, National Ovarian Cancer Coalition, Stafford, TX, 3/3/2006

Progress and Treatment of Ovarian Cancer, National Ovarian Cancer Coalition, American Cancer Society, National Ovarian Cancer Coalition, American Cancer Society, Austin, TX, 3/20/2006

What you need to know - Hereditary Breast and Ovarian Cancer, UT M D Anderson Cancer Center and The San Antonio Chapter of Hadassah, San Antonio, TX, 10/26/2006

Progress and Treatment for Ovarian Cancer, UTMB - CME Grand Rounds, Galveston, TX, 2/14/2007

Moderator - Stump the Professor, 37th Annual Meeting of the Felix Rutledge Society, Houston, TX, 6/13/2007

Ovarian Cancer Advisory Panel, Physician Oncology Education Program, Ovarian Cancer Advisory Panel Meeting, Texas Medical Association, Austin, TX, 12/10/2007

Cervical Cancer Update Including the Role of Vaccines, SGO-Society of Gynecologic Oncologist, Educational Concepts Group, LLC, Oncobeat SGO: Reporting the News.Beating Cancer, San Antonio, TX, 2/8/2009

Wolf, JK. Strategies for the Management of Platinum-Resistant Ovarian Cancer, 41st Annual Meeting on Women's Cancer Society of Gynecologic Oncologist, CBCE - University of North Texas Health Science Center at Fort Worth, Center for Biomedical Continuing Education, San Francisco, CA, 3/15/2010

Ovarian Cancer, Women's Cancer Awareness Conference, Methodist Healthcare System, San Antonio, TX, 9/30/2010

Gynecologic Oncology Overview, Grand Rounds, Beaumont Hospital, Beaumont, TX, 4/17/1997
Abnormal Uterine Bleeding & Endometrial Cancer, Grand Rounds, St. Frances Cabrini Hospital, Alexandria, LA, 8/24/1999

Gynecologic Oncology Overview, Grand Rounds, Nacogdoches/San Augustine Medical Society, Nacogdoches, TX, 11/10/1999

Gene Therapy for Gynecologic Malignancies, University of Minnesota Fellowship Program, Minneapolis, MN, 12/14/1999

Gynecologic Cancers: Diagnosis, Treatment & Outcomes-Where We've Been & Where We're Going, 2nd Annual "Closing Gaps & Opening Doors Conference for Working Women, U.S. Department of Labor, Women's Bureau Region VI, Austin, TX, 10/5/2000

Gynecologic Cancers: Diagnosis, Treatment & Outcomes-Where We've Been & Where We're Going, Grand Rounds, Christus Spohn Health System Tumor Conference, Corpus Christi, TX, 9/20/2000

Talk-back Session - Moderator, Wet State Theater, Alley Theater, UT M D Anderson Cancer Center & the Stanford Foundation, Austin, TX, 5/31/2001

Interferon-g in the Management of Ovarian Cancer clinical Advisory Program, Advisory Program, InterMune Pharmaceuticals, Houston, TX, 6/21/2001

Current and New Treatment Strategies for Ovarian Cancer, CME, University of Medicine & Dentistry of New Jersey, Medical School, Newark, NJ, 3/27/2002

Ethical Delima's in Clinical Trials, John J. Molitar Lectureship, University of California, Irvine, CA,

10/30/2002

The Application of Gene Therapy for Gynecologic Malignancies, Texas Medical Center Gene Therapy Symposium, Texas Medical Center, Houston, TX, 11/11/2002

Indication for and Value of Screening for Ovarian Cancer, CME, Inova Institute of Research & Education, Fairfax, VA, 11/15/2002

Treatment of recurrent Ovarian Cancer, CME, Walter Reed Army Medical Center, Bethesda, MD, 12/4/2002

Novel Therapeutics for Endometrial Cancer, 2003 SGO Winter Meeting, Society of Gynecologic Oncologist, Breckenridge, CO, 3/7/2003

Physician Advisor for Gynecological Cancer Advisory Board, Novel Approaches to the Treatment of Gynecological Cancer, 2003 Oncology Forum, Fox Chase Cancer Center, Philadelphia, PA, 4/26/2003

Current & New Treatments for Ovarian Cancer, Cancer in Women: A Scientific Update in Prevention, Screening and Treatment for Ovarian Cancer, NOCC, Houston, TX, 1/1/2004

Management of Gynecologic Cancer, Sanofi-Synthelabo Oncology Health Science Advisory Board Meeting, Sanofi-Synthelabo Oncology, Dallas, TX, 4/24/2004

Controversies in Ovarian Cancer, ACOG Update, Audiotaped Tele-Conference, ACOG, Houston, TX, 5/14/2004

Health issues and risk factors for Breast and Gynecologic Cancers, Hadassah Check it Out program to educate young women in Houston Independent School District, Worthing High School, Houston, TX, 2/9/2005

Screening for Gynecologic Cancers, CME Memorial Hermann Southwest Hospital, Memorial Hermann Southwest Hospital, Houston, TX, 3/8/2005

The Role of COUP-TFII in Ovarian Cancer, Arthur M. Faris, Sr., MD Resident Research Day, Baylor College of Medicine, Obstetrics and Gynecology, Houston, TX, 5/6/2005

Translational Research from Bench to Bedside One Gynecologic Oncologist's Experience, Bench to Beside Symposium, NYU Medical Center, New York, NY, 5/20/2005

Progress and Treatment of Ovarian Cancer, MDACC Faculty Speakers Bureau, CME - OB/GYN Grand Rounds, St. David's Healthcare, Austin, TX, 10/18/2005

Progress and Treatment of Ovarian Cancer, MDACC Faculty Speakers Bureau, CME - University Hospital Grand Rounds, University Health Care System, Augusta, GA, 10/20/2005

Current and New Treatments for Ovarian Cancer, CME, Advocate Christ Hospital, Oak Lawn, IL, 1/12/2006

Menopause The Musical Out Loud - Breaking the Silence on Ovarian Cancer, National Ovarian Cancer Coalition, Matrix Graphix, and Ovarian Cancer National Alliance Aging Out Loud Tour, TOC Productions Inc., www.menopausethemusical.com, National Ovarian Cancer Coalition, Stafford, TX, 3/3/2006

Progress and Treatment of Ovarian Cancer, National Ovarian Cancer Coalition, American Cancer Society, National Ovarian Cancer Coalition, American Cancer Society, Austin, TX, 3/20/2006

The Ethics of Clinical Trials, University of Minnesota Gynecologic Oncology Consensus Conference, University of Minnesota, Minneapolis, MN, 5/8/2006

What you need to know - Hereditary Breast and Ovarian Cancer, UT M D Anderson Cancer Center and The San Antonio Chapter of Hadassah, San Antonio, TX, 10/26/2006

Progress and Treatment for Ovarian Cancer, UTMB - CME Grand Rounds, Galveston, TX, 2/14/2007
Comprehensive Management of Ovarian Cancer: Current Treatment and Maximizing Quality of Life, CME-Medical Communications Media, Novato Community Hospital, Novato, CA, 5/7/2007

Comprehensive Management of Ovarian Cancer: Current Treatment and Maximizing Quality of Life, Grand Rounds-Medical Communications Media, University of Pittsburgh, Pittsburgh, PA, 6/5/2007

Moderator - Stump the Professor, 37th Annual Meeting of the Felix Rutledge Society, Houston, TX, 6/13/2007

Ovarian Cancer Advisory Panel, Physician Oncology Education Program, Ovarian Cancer Advisory Panel Meeting, Texas Medical Association, Austin, TX, 12/10/2007

Lecturer: Teal Lunch for Life, "Ovarian Cancer: Top Ten Questions What you really need to know..," benefiting Blanton-Davis Ovarian Cancer Research Program, San Antonio, TX, September 10, 2008

Lecturer: E2 Communications-Opinions in Gyn Malignancies: An Interactive Forum and KOL Focus Group, Las Vegas, NV, October 18, 2008

Treatment of Ovarian Cancer - 21st Century and Beyond, Grand Rounds, UC Davis Medical Center, Gynecologic Oncology, Sacramento, CA, 12/17/2008

Lecturer: Shell Health - Shell Oil Company, Prevention and Gynecological Oncology, Houston, TX, April 6, 2009

Lecturer: Raising Ovarian Cancer Awareness to Increase Survival Rates; NOCC, Media Blitz in New York, NY, April 22-23, 2009

Speaker, Teal Lunch for Life, "Ovarian Cancer: What you need to know and how you can help..,"

benefiting Blanton-Davis Ovarian Cancer Research Program, San Antonio, TX, Sept. 9, 2009

Speaker, Key to the Cure Benefit, "Ovarian Cancer, Raise Awareness"; NOCC & Saks 5th Avenue-Austin, Austin, TX, September 17, 2009

Cervical Cancer Update Including the Role of Vaccines, SGO-Society of Gynecologic Oncologist, Educational Concepts Group, LLC, Oncobeat SGO: Reporting the News.Beating Cancer, San Antonio, TX, 2/8/2009

Gynecologic Cancers: Uterine Cancer, CME: Update on Endometrial Cancer, Citizens Medical Center, Office of Continuing Medical Education, Victoria, TX, 1/11/2010

Speaker, CME/CNE Ovarian Cancer Knowledge Video, Texas Medical Association, Ovarian Cancer Advisory Panel Meeting, Austin, TX, January 25, 2010

Wolf, JK. Strategies for the Management of Platinum-Resistant Ovarian Cancer, 41st Annual Meeting on Women's Cancer Society of Gynecologic Oncologist, CBCE - University of North Texas Health Science Center at Fort Worth, Center for Biomedical Continuing Education, San Francisco, CA, 3/15/2010

Ovarian Cancer, Women's Cancer Awareness Conference, Methodist Healthcare System, San Antonio, TX, 9/30/2010

PROFESSIONAL MEMBERSHIPS/ACTIVITIES

Professional Society Activities, with Offices Held National and International

American Association of Cancer Research

Member, 1996-present

Felix Rutledge Society

Member, 1996-present

Chairman, Program Committee, 1999

Co-Chairman, Program Committee, 2007

President, 2008-2009

Society of Gynecologic Oncology

Member, 1996-present

Member, Program Committee, 1999

Member, Government Relations Committee, 2002-2011

Co-Chair, Government Relations Committee, 2005-2011

American Society of Clinical Oncology

Member, 1997-present

American College of Obstetrics and Gynecology

Fellow, 1999-present

Gynecologic Oncology Group

Member, Developmental Therapeutics Committee, 2001-2011

Member, Phase I Subcommittee, 2004-2011

NEOMED Alumni Board

Rootstown, OH

Member 2008-present

Southern Regional Professional Development Conference for Women in Medicine and Research, Take charge of Your Life: Speak Up, Stand Out, and Stay Calm

Member, Planning Committee, 3/2007

American Gynecological & Obstetrical Society

Fellow, 11/2007-present

Southwest Oncology Group (SWOG), Seattle, WA

Member, 11/2010-2011

Local/State

Houston Gynecology & Obstetrics Society, Houston, TX

Member, 1996

Treasurer, 1998-2000

Vice President, 2001-2002

President-Elect, 2002-2003

President, 2003-2004

Member, 2004-2011

Ob-Gyn Alumni Association, The University of Texas Health Science Center at San Antonio, San Antonio, TX

Member, 1999

American Board of Obstetrics & Gynecology, Dallas, TX

Oral Board Examiner, 12/2008

Oral Examiner, 12/2009

Examiner, 12/2010

MEDIA: LOCAL AND NATIONAL

1. News Article on Women's Health On Alert Conference: Wiley, Miryam (Townsmen Correspondent)
Women and hormonal health - the expert views. The Wellesley Townsman: townonline.com, April 7, 2005
2. Lecturer, Breaking the Silence on Ovarian Cancer - Diagnosis and Treatment; NOCC, State of

Disease, Teleconference in Advance of Nation's Leading Cancer Meeting, Taped in New York, NY,
Televised Live Across the Nation, May 22-23, 2006

3. Lecturer, Breaking the Silence on Ovarian Cancer - Diagnosis and Treatment; NOCC Media Initiative Magazine Interview, Interviewed in New York, NY, Fitness, MEDIZine's Healthy Living, Family Circle, Prevention, Cosmopolitan, Glamour, Woman's Day, O Magazine, March 11-13, 2007
4. Lecturer, Breaking the Silence on Ovarian Cancer Campaign, NOCC Media Alert Blitz on the Consensus of Ovarian Cancer; Teleconference in Advance of Nation's Leading Cancer Meeting, Taped in Houston, Texas, Televised Live Across the Nation, June 25, 2007
5. Dr. Oz Show appearance, Birth Control Pills and Risk of Ovarian Cancer, March 2012
6. I Heart Radio, "Preview of Highlights of San Antonio Breast Cancer Society Meeting", December 2013

COMMUNITY

1. Founder, Sprint for Life Fun Run, Raised Well Over \$3.6 Million to Date For Cancer Research, 1998-Present
2. Foundation Event – Development Reception for Banner MD Anderson Cancer Center, November 3, 2011
3. Foundation Event – Presentation at Vi Community, Scottsdale, Arizona 02/2012
4. Banner Health Foundation Lunch - JoAnn Orefice, Pat McKennon and Pat Carbone Tour and Lunch, March 30, 2012
5. Foundation Event – Freeport McMoRan Employee Campaign Launch, Phoenix, AZ , April 6, 2012
6. Surgery Grand Rounds, Banner Good Samaritan Hospital, Gynecologic Oncology 2012 Updates, Phoenix, AZ, March 2012
7. Foundation Event – Bill and Anne Smith Reception, Sedona, AZ April 21, 2012
8. Foundation Event – Presentation at Vi Community, Scottsdale, Arizona 09/12/2012
9. Speaker at 4th Annual Run/Walk for Ovarian Cancer, Break the Silence, NOCC 09/23/2012
10. Speaker at Association of Physician Assistants in Oncology, 2012 Annual Conference, Scottsdale, AZ 10/13/2012
11. Obesity and Cancer, Banner Gateway Medical Center Bariatric Grand Rounds, 02/2013
12. Advanced Leadership Program for Physicians, Banner Health, 2012-2013
13. Principal-Investigator, Various Donors, UT M. D. Anderson Cancer Center, 1999-Present, \$324,834
14. Selected 2013 *Top 50 Most Influential Women in Business*

NATIONAL PROFESSIONAL LECTURES/TALKS

Lecturer: **Strengthening Her Fight in the Battle Against Ovarian Cancer; Physicians Connect-Tibotec (Doxil) Pharmaceuticals & MediMedia**

Houston, TX, October 11, 2005
 Woodlands, TX October 12, 2005
 Moline, IL, October 25, 2005
 Monrovia, CA, October 27, 2005
 Grand Rapids, MI, December 15, 2005
 Kansas City, MO, January 10, 2006
 Houston, TX, October 17, 2006
 Oklahoma City, OK, November 14, 2006
 Woodlands, TX, April 23, 2007
 Oklahoma City, OK, May 8, 2007
 Houston, TX, June 12, 2007
 Houston, TX, June 19, 2007
 Houston, TX (MDACC), June 22, 2007
 Houston, TX, October 17, 2007
 Houston, TX, December 5, 2007
 Houston, TX, June 6, 2008
 Houston, TX, May 14, 2009

Lecturer: **Latest Developments in HPV-Related Diseases and Cervical Cancer; Merck i-Med Conference**

Lubbock, TX, September 26, 2006
 Dallas, TX, October 10, 2006
 Tyler, TX, October 24, 2006
 Harvey, LA, November 16, 2006
 Beaumont, TX, November 20, 2006
 Snyder, TX, November 21, 2006
 Bedford, TX, January 18, 2007
 Denver, CO, January 30, 2007
 Houston, TX, February 13, 2007
 Baytown, TX, February 20, 2007
 Houston, TX, March 14, 2007
 Austin, TX, March 28, 2007
 Arlington, TX, May 14, 2007
 Houston, TX (MDACC), May 18, 2007

Webster, TX, May 23, 2007
Woodlands, TX, June 7, 2007
Dallas, TX, June 8, 2007
Chicago, IL, July 23, 2007
Nacogdoches, TX, October 30, 2007
Houston, TX, November 11, 2007
San Antonio, TX, November 14, 2007
Dallas, TX, December 4, 2007
Dallas, TX, December 14, 2007
Grapevine, TX, February 4, 2008
San Antonio, TX, February 18, 2008
San Angelo, TX, February 19, 2008
Nacogdoches, TX, February 28, 2008
Hutchinson, KS, May 12, 2008

Lecturer: **The Management of Cervical Cancer: Focus on Hycamtin; Advanced Communication and Education (ACE) - Glaxo Smith Klein (GSK)**

Beaumont, TX, October 30, 2006
Corpus Christi, TX, November 27, 2006
Lafayette, LA, November 28, 2006
Lake Charles, LA, April 2, 2007

Grand Rounds Speaker: **Comprehensive Management of Ovarian Cancer: Current Treatment and Maximizing Quality of Life; Medical Communications Media Bureau**

Casper, WY, September 11, 2007
Pensacola, FL, October 9, 2007
Sugarland, TX, November 9, 2007
Houston, TX, December 4, 2007
Victoria, TX, December 5, 2007
Birmingham, AL, April 1, 2008
Kansas City, MO, May 7, 2008
St. Petersburg, FL, August 21, 2008
Victoria, TX, December 3, 2008
Newport Beach, CA, December 4, 2008

Lecturer: **The Treatment of Platinum-Sensitive Advanced Ovarian Cancer; Lilly Lecturer Bureau**

Houston, TX, April 3, 2007
Harlingen, TX, 12pm & 7pm, Jan 31, 2008
McAllen, TX, March 26, 2008
Brownsville, TX, March 26, 2008
Jacksonville, FL, April 23, 2008
Houston, TX, May 5-6, 2008
Fort Worth, TX, May 14, 2008
Wichita Falls, TX, May 14, 2008
Houston, TX, May 15, 2008
San Antonio, TX, May 28, 2008
Houston, TX, June 4, 2008
San Antonio, TX, July 2, 2008
Beaumont, TX, July 23, 2008
Fort Worth, TX, August 27, 2008
Wichita Falls, TX, August 27, 2008
Indianapolis, IN, (3-talks), September 3, 2008

Corpus Christi, TX, September 17, 2008

Laredo, TX, September 17, 2008

San Antonio, TX, October, 22, 2008

Temple, TX, May 22, 2009

Laredo, TX, May 27, 2009

McAllen, TX, May 28, 2009

Houston, TX, June 4, 2009

Houston, TX, June 17, 2009

Beaumont, TX, August 6, 2009

CV updated; 09/24/2014

Judith K Wolf, MD

Updated 7/6/2016

Exhibit B

- “A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis.” *British Journal of Diseases of the Chest* 73 (1979): 285–88. [https://doi.org/10.1016/0007-0971\(79\)90054-8](https://doi.org/10.1016/0007-0971(79)90054-8).
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- . "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 27, no. 3 (2018): 248–57. <https://doi.org/10.1097/CEJ.0000000000000340>.
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Exhibit 14

Judith K. Wolf, M.D.

Page 1

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW JERSEY

IN RE: JOHNSON & :
JOHNSON TALCUM POWDER :
PRODUCTS MARKETING, :
SALES PRACTICES, AND :
PRODUCTS LIABILITY : CASE NO. 16-2738
LITIGATION : (FLW) (LHG)
:
THIS DOCUMENT RELATES :
TO ALL CASES :
:
MDL Docket No. 2738 :

- - -

Monday, January 7, 2019

- - -

Videotaped Oral Deposition of
JUDITH K. WOLF, M.D. taken pursuant to
notice, was held at the Hilton Austin, 500
East 4th Street, Austin, Texas, beginning at
9:08 a.m., on the above date, before Micheal
A. Johnson, Registered Diplomate Reporter,
Certified Realtime Reporter, and Notary
Public for the State of Texas.

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Judith K. Wolf, M.D.

Page 2	Page 4
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Page 3	Page 5
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2 (Pages 2 to 5)

Golkow Litigation Services - 877.370.DEPS

Judith K. Wolf, M.D.

Page 6				Page 8			
1	DEPOSITION EXHIBITS JUDITH K. WOLF, M.D. January 7, 2019			1	DEPOSITION EXHIBITS JUDITH K. WOLF, M.D. January 7, 2019		
2				2			
3				3			
4	NUMBER	DESCRIPTION	MARKED	4	NUMBER	DESCRIPTION	MARKED
5	Exhibit 1	Notice of Oral and	11	5	Exhibit 17	Genital use of talc and	247
6		Videotaped Deposition of		6		risk of ovarian cancer:	
7	Exhibit 2	Reprint from UpToDate,	12	7	Exhibit 18	Ovarian, Fallopian Tube,	272
8		Evidence-based medicine		8		and Primary Peritoneal	
9	Exhibit 3	IARC Monographs on the	31	9		Cancer Prevention (PDQ)	
10		Evaluation of		10	Exhibit 19	African-Americans and	294
11	Exhibit 4	Reproductive Sciences,	35	11		Hispanics Remain at	
12		Original Manuscripts		12		Lower Risk of Ovarian	
13	Exhibit 5	Invoices for TALC MDL	36	13		Cancer Than Non-Hispanic	
14	Exhibit 6	Curriculum Vitae	52	14		Whites after Considering	
15	Exhibit 7	Rule 26 Expert Report of	66	15	Exhibit 20	The Future of Ovarian	350
16	Exhibit 8	Rule 26 Expert Report of	100	16		Cancer Diagnosis Is Now	
17		Ellen Blair Smith, MD		17	Exhibit 21	How to find the best	353
18	Exhibit 9	FDA.gov, Ingredients,	128	18		doctor for ovarian	
19	Exhibit 10	Excerpt from Arsenic,	157	19	Exhibit 22	Arsenic, Metals, Fibres,	427
20		Metals, Fibres, and		20		and Dusts, IARC	
21		Dusts, IARC Monographs		21		Monographs on the	
22		on the Evaluation of		22		Evaluation of	
23		Carcinogenic Risks to		23		Carcinogenic Risks to	
24		Humans		24		Humans	
Page 7				Page 9			
1	DEPOSITION EXHIBITS JUDITH K. WOLF, M.D. January 7, 2019			1	PROCEEDINGS		
2				2	THE VIDEOGRAPHER: Here begins		
3				3	the deposition of Dr. Judy Wolf.		
4	NUMBER	DESCRIPTION	MARKED	4	Today's date is January 7th, 2019.		
5	Exhibit 11	The Association Between	198	5	The time is 9:08 a.m.		
6		Talc Use and Ovarian		6	Will the court reporter please		
7		Cancer, A Retrospective		7	swear in the witness.		
8	Exhibit 12	The relationship between	213	8	JUDITH K. WOLF, M.D.,		
9		perineal cosmetic talc		9	called as a witness, having been duly sworn		
10		usage and ovarian talc		10	by a Notary Public, was examined and		
11	Exhibit 13	IARC Monographs on the	224	11	testified as follows:		
12		Evaluation of		12	EXAMINATION		
13		Carcinogenic Risks to		13	BY MS. BROWN:		
14		Humans, Volume 93,		14	Q.	Good morning, Dr. Wolf.	
15	Exhibit 14	April 1, 2014, Letter,	233	15	A.	Good morning.	
16		Steven Musser to Samuel		16	Q.	My name is Ally Brown and I	
17	Exhibit 15	American Association for	238	17		represent Johnson & Johnson, and I'll start	
18		Cancer Research,		18		with some questions for you here today.	
19		Research Article,		19		Okay?	
20		Association between Body		20	A.	Okay.	
21		Powder Use and Ovarian		21	Q.	Have you ever been deposed	
22		Cancer: The African		22		before?	
23		American Cancer		23	A.	One time.	
24	Exhibit 16	Perineal Talc Use and	245	24	Q.	And when was that?	
		Ovarian Cancer, A					
		Systematic Review and					
		Meta-Analysis					

3 (Pages 6 to 9)

Judith K. Wolf, M.D.

Page 10	Page 12
<p>1 A. That was -- I want to say, was</p> <p>2 nearly three years ago. It was a wrongful</p> <p>3 termination case at a hospital I used to</p> <p>4 work.</p> <p>5 Q. And were you the plaintiff in</p> <p>6 that case?</p> <p>7 A. No.</p> <p>8 Q. Okay. Were you a witness in</p> <p>9 that case?</p> <p>10 A. A witness.</p> <p>11 Q. Okay. And you're probably</p> <p>12 familiar with some of the rules of a</p> <p>13 deposition, having done this not too long</p> <p>14 ago, but I'll just remind you a little bit.</p> <p>15 A. Okay.</p> <p>16 Q. We'll try and talk one at a</p> <p>17 time, so that the court reporter can get down</p> <p>18 all of my questions and all of your answers.</p> <p>19 Do you understand that you are under oath</p> <p>20 here today same as if you were in a court of</p> <p>21 law?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. If you don't understand</p> <p>24 one of my questions, will you let me know?</p>	<p>1 today, you were -- the attorney representing</p> <p>2 plaintiffs provided me with a number of</p> <p>3 documents in request to this notice that I'd</p> <p>4 like to mark and ask you about.</p> <p>5 A. Okay.</p> <p>6 Q. And so the first one we'll mark</p> <p>7 as Exhibit 2 to your deposition.</p> <p>8 (Deposition Exhibit 2 marked</p> <p>9 for identification.)</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Which is an UpToDate printout</p> <p>12 from January 5th, 2019.</p> <p>13 A. Yes.</p> <p>14 Q. We only have one copy, so let</p> <p>15 me hand it to you and ask you to describe</p> <p>16 what Exhibit 2 is.</p> <p>17 A. This is an article from</p> <p>18 UpToDate that describes what evidence-based</p> <p>19 medicine is, which is -- I provided because</p> <p>20 this is how I reviewed the subject and how I</p> <p>21 review any subject when I'm looking to treat</p> <p>22 a patient or taking care of a patient or</p> <p>23 working on a research project, and I thought</p> <p>24 that this was a good outline and description</p>
Page 11	Page 13
<p>1 A. Yes.</p> <p>2 Q. And if you go ahead and answer</p> <p>3 them, is it fair to assume you understood</p> <p>4 what I was asking?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. We'll take breaks</p> <p>7 throughout the day. It's not a marathon, so</p> <p>8 just let me know if you need a break and</p> <p>9 we'll be happy to accommodate you. Okay?</p> <p>10 A. Okay.</p> <p>11 Q. I'm handing you, Dr. Wolf, what</p> <p>12 we have marked as Exhibit 1 to your</p> <p>13 deposition, which is the notice of your</p> <p>14 deposition.</p> <p>15 (Deposition Exhibit 1 marked</p> <p>16 for identification.)</p> <p>17 BY MS. BROWN:</p> <p>18 Q. Have you seen this document</p> <p>19 before?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. And when was that?</p> <p>22 A. I saw it several days ago. I</p> <p>23 can't remember exactly when.</p> <p>24 Q. Okay. And prior to starting</p>	<p>1 of what I do.</p> <p>2 Q. Do you consider UpToDate to be</p> <p>3 a reliable source in your field?</p> <p>4 A. I think it's a --</p> <p>5 MS. O'DELL: Object to form.</p> <p>6 A. I believe it's a good starting</p> <p>7 place. If I read something on UpToDate and I</p> <p>8 want something more in depth, the first thing</p> <p>9 I usually do is go to the references and look</p> <p>10 at those. If -- and if I want more</p> <p>11 information and there's an UpToDate, I'll do</p> <p>12 a general PubMed literature search to find</p> <p>13 other articles.</p> <p>14 BY MS. BROWN:</p> <p>15 Q. As part of your methodology in</p> <p>16 your report that we're here to talk about</p> <p>17 today in the MDL, did you employ the</p> <p>18 evidence-based medicine approach described in</p> <p>19 Exhibit 2?</p> <p>20 A. Yes.</p> <p>21 Q. And describe that for us</p> <p>22 briefly, if you would.</p> <p>23 A. So first is formulating a</p> <p>24 question and the question is, does talcum</p>

4 (Pages 10 to 13)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 14</p> <p>1 powder product cause ovarian cancer? And</p> <p>2 then the next part is finding the available</p> <p>3 evidence, which is, for me, looking at the</p> <p>4 literature that I had at my house to start,</p> <p>5 going on PubMed and searching literature,</p> <p>6 looking at references from those, going --</p> <p>7 finding more literature from the references</p> <p>8 that I pulled. Some references were provided</p> <p>9 by the attorneys, some other information that</p> <p>10 I asked for, they provided. And so trying to</p> <p>11 go through as many sources as I could find,</p> <p>12 to find as much information about the topic</p> <p>13 that I could find, both in human studies and</p> <p>14 in vitro studies and in animal studies.</p> <p>15 Q. And so if I understand your</p> <p>16 methodology, it was first formulating a</p> <p>17 question?</p> <p>18 A. Yes.</p> <p>19 Q. Is that right? And the</p> <p>20 question at issue as it relates to this MDL</p> <p>21 report was, does genital application of</p> <p>22 talcum powder cause cancer; is that right?</p> <p>23 A. Does genital -- does talcum</p> <p>24 powder product cause ovarian cancer.</p>	<p style="text-align: right;">Page 16</p> <p>1 but if there's talcum powder in them, yes.</p> <p>2 Q. Okay. What about tampons or</p> <p>3 other feminine products that contain talcum</p> <p>4 powder? Are you including that in your</p> <p>5 definition of a "talcum powder product"?</p> <p>6 A. Again, I haven't really thought</p> <p>7 about tampons as containing talcum powder as</p> <p>8 a possibility, so I would say I hadn't</p> <p>9 considered that.</p> <p>10 Q. Okay. What about talc-dusted</p> <p>11 condoms? Are you including that in your</p> <p>12 definition of a "talcum powder product"?</p> <p>13 A. I am, but my understanding is,</p> <p>14 that since the '90s, that practice has</p> <p>15 stopped because of concerns.</p> <p>16 Q. And tell me what you're relying</p> <p>17 on for that understanding.</p> <p>18 A. I have a reference in my</p> <p>19 report. I have to look up the name of the</p> <p>20 author.</p> <p>21 Q. Okay. And the reference in</p> <p>22 your report is actually to an internal PCP</p> <p>23 document. Is that what you're relying on for</p> <p>24 your understanding that condoms no longer</p>
<p style="text-align: right;">Page 15</p> <p>1 Q. That's the question that you</p> <p>2 endeavored to answer in your report?</p> <p>3 A. Yes.</p> <p>4 Q. Is that right?</p> <p>5 A. Yes.</p> <p>6 Q. And when you say talcum -- does</p> <p>7 talcum powder cause ovarian cancer, do you</p> <p>8 have a particular product in mind?</p> <p>9 A. I'm thinking about talcum</p> <p>10 powder product in general.</p> <p>11 Q. And how do you define a "talcum</p> <p>12 powder product"?</p> <p>13 A. Anything that comes in a powder</p> <p>14 form that people might apply to their body or</p> <p>15 someone else's body.</p> <p>16 Q. What about deodorizing sprays</p> <p>17 that contain talcum powder? Do you include</p> <p>18 that in your definition?</p> <p>19 A. I would include that in my</p> <p>20 definition.</p> <p>21 Q. Okay. What about soaps that</p> <p>22 contain talcum powder? Would you include</p> <p>23 that in your definition as well?</p> <p>24 A. I hadn't thought about that,</p>	<p style="text-align: right;">Page 17</p> <p>1 contain talcum powder?</p> <p>2 A. No. Well, can I look at my</p> <p>3 report for a second?</p> <p>4 Q. Absolutely.</p> <p>5 (Witness reviews document.)</p> <p>6 A. There are actually references</p> <p>7 above the PCP report, talking about concerns</p> <p>8 of ovarian cancer and talc on condoms, Kang,</p> <p>9 Griffin and Ellis, Casper and Chandler.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. And for the record, Doctor,</p> <p>12 what page are you on?</p> <p>13 A. I'm on page 5.</p> <p>14 Q. Okay. And your understanding</p> <p>15 that condoms no longer are dusted with talc</p> <p>16 comes from Kang, Griffin and Ellis 1992, and</p> <p>17 Casper and Chandler 1995, as well as an</p> <p>18 internal PCPC document and McCullough in</p> <p>19 1996; is that right?</p> <p>20 A. My understanding that there was</p> <p>21 concern about talcum powder on condoms is</p> <p>22 from the Kang, the Griffin and the Casper</p> <p>23 articles, and then my understanding about</p> <p>24 stopping dust in condoms was from the PCP</p>

5 (Pages 14 to 17)

Judith K. Wolf, M.D.

Page 18	Page 20
<p>1 document and the McCullough document.</p> <p>2 Q. Have you reviewed the</p> <p>3 epidemiology as it relates to whether or not</p> <p>4 there is an increased risk for ovarian cancer</p> <p>5 as a result of talc-dusted condoms?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. The papers, the Kang, the</p> <p>9 Griffin and the Casper paper, that's part of</p> <p>10 what they were looking at.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. And are you familiar with what</p> <p>13 the conclusion of the body of studies looking</p> <p>14 at talc-dusted condoms in ovarian cancer</p> <p>15 conclude?</p> <p>16 MS. O'DELL: Dr. Wolf, if</p> <p>17 you -- you have your records here. If</p> <p>18 you'd like to look at them, you're</p> <p>19 certainly welcome to do that.</p> <p>20 THE WITNESS: Let me get that.</p> <p>21 BY MS. BROWN:</p> <p>22 Q. Doctor, if you would, just</p> <p>23 identify the document you're looking at for</p> <p>24 us on the record.</p>	<p>1 directly talk about ovarian cancer, but the</p> <p>2 fact that the powder causes inflammation</p> <p>3 would lead me to be concerned about that.</p> <p>4 Q. Okay. And we're going to talk</p> <p>5 about inflammation. But you cited this Kang</p> <p>6 paper for the proposition that concerns were</p> <p>7 raised in the medical literature regarding</p> <p>8 ovarian cancer for talc being used on</p> <p>9 condoms. Does this paper speak to that in</p> <p>10 your mind, Doctor?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form, asked and answered.</p> <p>13 A. It specifically talks about</p> <p>14 inflammation from this, which inflammation is</p> <p>15 related to ovarian cancer.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. Is it your understanding,</p> <p>18 Doctor, that all inflammation leads to</p> <p>19 ovarian cancer?</p> <p>20 A. It's my understanding, from</p> <p>21 reviewing the literature and my own knowledge</p> <p>22 from practicing GYN oncology and doing the</p> <p>23 research in it over the years, is that it's</p> <p>24 more the concern of chronic inflammation</p>
Page 19	Page 21
<p>1 A. So I'm looking at the Kang,</p> <p>2 Griffin and Ellis paper right now.</p> <p>3 Q. Okay. Great.</p> <p>4 (Witness reviews document.)</p> <p>5 A. Now I'm looking at the Casper</p> <p>6 paper.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. And before we move the -- move</p> <p>9 from the Kang paper, Doctor, is there</p> <p>10 anything in the Kang paper that informs your</p> <p>11 view about whether or not there's an</p> <p>12 increased risk of ovarian cancer with</p> <p>13 talc-dusted condoms?</p> <p>14 A. This paper is just looking at</p> <p>15 the pathologic changes from talc powder on</p> <p>16 gloves or condoms and is looking at</p> <p>17 pathologic changes in the intraabdominal</p> <p>18 cavity. It doesn't specifically look at the</p> <p>19 risk of ovarian cancer.</p> <p>20 Multiple other papers, both</p> <p>21 prior and subsequent to this, though,</p> <p>22 indicate that inflammation is an important</p> <p>23 part in the development of ovarian cancer,</p> <p>24 and so it does -- this paper does not</p>	<p>1 versus acute inflammation.</p> <p>2 When I look at the pathology of</p> <p>3 ovarian tumors, sometimes we see a lot of</p> <p>4 chronic, sometimes we see a mix of chronic</p> <p>5 and acute inflammation, sometimes you don't</p> <p>6 see inflammation. That doesn't mean it's not</p> <p>7 there; it just means it's not there in the</p> <p>8 slide that you're looking at. But in</p> <p>9 general, more concern about chronic</p> <p>10 inflammation.</p> <p>11 Q. Because, Doctor, you would</p> <p>12 agree, that you can certainly have</p> <p>13 inflammation that does not cause cancer,</p> <p>14 right?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. Inflammation itself doesn't</p> <p>18 always cause cancer. However, inflammation</p> <p>19 has been correlated with the development of</p> <p>20 ovarian cancer in multiple studies, and since</p> <p>21 the '30s, it's been suggested in the</p> <p>22 implication of all cancers -- or many cancers</p> <p>23 anyway. I'll stop there.</p> <p>24</p>

6 (Pages 18 to 21)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 22</p> <p>1 BY MS. BROWN: 2 Q. Would you agree, Doctor, that 3 the inflammation that was being caused by 4 powders on surgical gloves was not 5 inflammation that was -- was suspected of 6 leading to cancer? 7 MS. O'DELL: Object to the 8 form. 9 A. I can't -- I don't know that I 10 can say that, because if there's deposits of 11 talc from the surgical gloves into the 12 abdominal cavity and it stays there because 13 it's not dissolved, that can lead to chronic 14 inflammation. 15 BY MS. BROWN: 16 Q. Do you have any -- can you cite 17 any evidence in the medical literature of 18 talc from surgical gloves causing a 19 procancerous inflammatory response? 20 MS. O'DELL: Object to the 21 form. 22 A. Can you define for me what you 23 mean by a "procancer inflammatory response"? 24 BY MS. BROWN:</p>	<p style="text-align: right;">Page 24</p> <p>1 BY MS. BROWN: 2 Q. Just for the record, Doctor, 3 the lawyer for the plaintiffs has asked that 4 you be able to look at the transcript of my 5 questions and your answers, to assist you 6 with your testimony under oath here today; is 7 that right? 8 MS. O'DELL: No, actually, 9 she's -- she's had it there, not to 10 assist her, but just to make sure 11 she's read the -- understood the 12 question correctly. I'll put it that 13 way. You can answer. 14 BY MS. BROWN: 15 Q. Just for the record, you'll be 16 looking at the realtime questions and answers 17 and testifying here today; is that right? 18 A. That's my understanding, yes. 19 So now I'm going to have to ask 20 you to repeat the question. 21 Q. Fair enough, Doctor. We were 22 talking a little bit about talcum powder on 23 surgical gloves. Do you remember that? 24 A. Yes.</p>
<p style="text-align: right;">Page 23</p> <p>1 Q. Sure. Can you cite us any 2 evidence in the medical literature that talc 3 from surgical gloves led to chronic 4 inflammation that caused cancer. 5 MS. O'DELL: Object to the 6 form. 7 A. I can cite literature that talc 8 from surgical gloves causes inflammation and 9 there is the concern that it leads to cancer. 10 BY MS. BROWN: 11 Q. Okay. And for the proposition, 12 the second part of what you're testifying 13 about, the concern that surgical gloves were 14 causing, not just granulomas or adhesions or 15 foreign body reactions, but cancer, but what 16 literature are you relying on for that 17 proposition? 18 MS. O'DELL: Object to the 19 form. Excuse me just for a minute. 20 Micheal, would you make the screen -- 21 I don't know how that -- 22 THE WITNESS: So I can see it. 23 MS. O'DELL: Yes. 24</p>	<p style="text-align: right;">Page 25</p> <p>1 Q. And is it your opinion that 2 talcum powder that was used on surgical 3 gloves could lead to cancer? 4 A. It's my opinion that talcum 5 powder generally has a concern for 6 carcinogenesis, and because it was known to 7 cause inflammation in adhesions, it has been 8 removed from surgical gloves and from 9 condoms. 10 Q. And what are you relying on for 11 your understanding that dusting powders were 12 removed from surgical gloves because of a 13 concern for cancer? 14 A. I believe that we've already 15 talked about that, the PCPC report that's 16 referenced on page 5 in my report. 17 Q. Okay. So that's an internal 18 company document that you cite in connection 19 with condoms, right? 20 A. Yes. 21 Q. Okay. And so my question was a 22 little bit different, which is, what 23 scientific literature are you relying on to 24 support your opinion that dusting powder on</p>

7 (Pages 22 to 25)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 26</p> <p>1 surgical gloves can lead to cancer?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. I'm going to give you the same</p> <p>5 answer that I think I've given before is</p> <p>6 that, the concern is that dusting powder on</p> <p>7 surgical gloves has been shown to cause</p> <p>8 inflammation and then that inflammation can</p> <p>9 lead to cancer.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. And my question's just a little</p> <p>12 bit different, which is, I'm asking you to</p> <p>13 identify the scientific literature on which</p> <p>14 you rely for that opinion, and "that opinion"</p> <p>15 being that powders on surgical gloves can</p> <p>16 cause cancer?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form, asked and answered. That's</p> <p>19 probably the third time the question's</p> <p>20 been repeated.</p> <p>21 Dr. Wolf, you're welcome to</p> <p>22 respond to the question.</p> <p>23 A. I have the same answer that I</p> <p>24 gave before. And powder has been removed</p>	<p style="text-align: right;">Page 28</p> <p>1 A. So the studies suggest -- or</p> <p>2 show inflammation after talcum powder on --</p> <p>3 or talc, talcum powder product on surgical</p> <p>4 gloves, dusting powder, and therefore it was</p> <p>5 taken off the market. I am not aware of a</p> <p>6 study where talcum-dusted, dusting powdered</p> <p>7 gloves was used to see if it caused cancer.</p> <p>8 I believe that would be unethical. And so</p> <p>9 the concern that there is inflammation was</p> <p>10 enough that that was pulled off the market.</p> <p>11 Q. Okay. And when you talk about</p> <p>12 "unethical," you're talking about running a</p> <p>13 randomized, controlled clinical trial, right?</p> <p>14 A. A prospective study of any</p> <p>15 kind.</p> <p>16 Q. Sure. And certainly it would</p> <p>17 not be unethical to look at people who have</p> <p>18 had operations with surgical gloves to study</p> <p>19 this issue, correct?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. So you're -- could you</p> <p>23 retrospectively look and see if people who</p> <p>24 had surgery with powdered gloves got cancer</p>
<p style="text-align: right;">Page 27</p> <p>1 from surgical gloves because of the concern</p> <p>2 of adhesions and inflammation.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. I understand that testimony</p> <p>5 perfectly. And maybe we're just not</p> <p>6 connecting, Dr. Wolf. I understand your</p> <p>7 opinion, and what I'm asking is, for the</p> <p>8 scientific support for that opinion. And so</p> <p>9 what information are you relying on that</p> <p>10 dusting powders on surgical gloves can cause</p> <p>11 cancer?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form, asked and answered the sixth</p> <p>14 time.</p> <p>15 A. My understanding is what you're</p> <p>16 asking me is, can I cite you a paper that</p> <p>17 says that dusting powder on surgical gloves</p> <p>18 causes cancer?</p> <p>19 BY MS. BROWN:</p> <p>20 Q. My question to you is, what is</p> <p>21 the scientific support, what articles in the</p> <p>22 scientific literature, what studies have you</p> <p>23 looked at that brings you to that conclusion?</p> <p>24 If it's a paper, then we'll take the paper.</p>	<p style="text-align: right;">Page 29</p> <p>1 more than those that did not? Is that what</p> <p>2 you're asking me?</p> <p>3 BY MS. BROWN:</p> <p>4 Q. Sure. What I'm trying to clear</p> <p>5 up is, you didn't mean to suggest this is an</p> <p>6 area of science that cannot be studied.</p> <p>7 Fair?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. My suggestion would be that it</p> <p>11 would be an area of study that would be</p> <p>12 challenging to study. I'm not saying it</p> <p>13 couldn't be. I'm saying it could be</p> <p>14 challenging.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. Have you reviewed, in</p> <p>17 connection with your opinions in this case,</p> <p>18 the reasoning of the FDA when they banned</p> <p>19 powders on surgical gloves?</p> <p>20 A. I don't recall that I have.</p> <p>21 Q. Are you aware of whether or not</p> <p>22 the FDA made a determination about whether or</p> <p>23 not the science supported your opinion here,</p> <p>24 that use of powders on gloves can lead to</p>

8 (Pages 26 to 29)

Judith K. Wolf, M.D.

Page 30	Page 32
<p>1 cancer?</p> <p>2 A. I don't recall.</p> <p>3 Q. Do you consider the FDA to be a</p> <p>4 reliable public health authority?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. I consider that the FDA does</p> <p>8 its best to be a reliable health authority.</p> <p>9 The FDA, or any agency, is not without the</p> <p>10 ability to make a wrong decision or a</p> <p>11 decision that they later change.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. Do you consider the work that</p> <p>14 scientists at the FDA do in connection with</p> <p>15 public health issues, to be important to</p> <p>16 consider in forming your opinions regarding</p> <p>17 scientific theories?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. I think it's a piece of</p> <p>21 information to consider.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. And as it relates to your</p> <p>24 opinion about dusting powders on surgical</p>	<p>1 to answer a question and pulled it today</p> <p>2 or -- or gave it today because they actually</p> <p>3 use very similar methods.</p> <p>4 Q. Do you consider the</p> <p>5 International Agency on the Research of</p> <p>6 Cancer to be a respected public health</p> <p>7 authority?</p> <p>8 A. I do.</p> <p>9 Q. Do you look to the research</p> <p>10 that the scientists at IARC do, when</p> <p>11 considering your own evaluation of scientific</p> <p>12 theories?</p> <p>13 A. I do.</p> <p>14 Q. Do you think that IARC is</p> <p>15 generally an impartial body that endeavors to</p> <p>16 do the best research it can on cancer?</p> <p>17 A. I do.</p> <p>18 Q. And have you considered IARC's</p> <p>19 conclusions as it relates to the opinions</p> <p>20 that you've provided in your report, your MDL</p> <p>21 report?</p> <p>22 A. Yes. I considered them amongst</p> <p>23 many things.</p> <p>24 Q. Sure. Is there anything</p>
Page 31	Page 33
<p>1 gloves, you have not had the opportunity to</p> <p>2 review the FDA's research on that score; is</p> <p>3 that fair?</p> <p>4 A. That's correct.</p> <p>5 Q. Another item, Doctor, that</p> <p>6 counsel for plaintiffs handed me before we</p> <p>7 began the deposition, I will mark as</p> <p>8 Exhibit 3, and it is the preamble to the IARC</p> <p>9 monograph -- IARC monographs from the</p> <p>10 evaluation of carcinogenic risk to humans.</p> <p>11 This is an amendment of January 2006.</p> <p>12 (Deposition Exhibit 3 marked</p> <p>13 for identification.)</p> <p>14 BY MS. BROWN:</p> <p>15 Q. I can hand you the copy we've</p> <p>16 marked. Let me know -- first of all, when</p> <p>17 did you review the preamble, Doctor?</p> <p>18 A. When I looked at the IARC</p> <p>19 monographs more than a year ago, I read the</p> <p>20 whole thing, but this preamble specifically I</p> <p>21 re-reviewed a few days ago when I pulled the</p> <p>22 UpToDate article about evidence-based</p> <p>23 medicine, to see how they review -- what</p> <p>24 methods they used to review a subject to try</p>	<p>1 different between the UpToDate source that</p> <p>2 you provided as Exhibit 2 and the preamble</p> <p>3 that you've directed us to on Exhibit 3?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 BY MS. BROWN:</p> <p>7 Q. That wasn't a great question.</p> <p>8 Do you find that Exhibit 2, the UpToDate</p> <p>9 summary of evidence-based medicine, is</p> <p>10 generally in concert with the preamble to the</p> <p>11 IARC monographs?</p> <p>12 A. I think in general, it is. I</p> <p>13 think that the UpToDate evidence-based</p> <p>14 medicine article is something that I as a MD,</p> <p>15 a clinician, a practicing doctor, this is how</p> <p>16 I think about questions. How IARC thinks</p> <p>17 about it may not be exactly the same, but the</p> <p>18 general principles are the same.</p> <p>19 Q. Is UpToDate a peer-reviewed</p> <p>20 publication, do you know, Doctor?</p> <p>21 A. It is a peer-reviewed</p> <p>22 publication. I would say it's -- it is.</p> <p>23 Q. And what knowledge do you have</p> <p>24 about the peer-reviewed process for the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 34</p> <p>1 UpToDate articles?</p> <p>2 A. I don't know their peer review</p> <p>3 process. I've never put any article into</p> <p>4 UpToDate. So I don't understand -- I don't</p> <p>5 know the details of it.</p> <p>6 Q. Okay. What basis do you have</p> <p>7 for saying that the UpToDate information</p> <p>8 you've provided as Exhibit 2 is peer</p> <p>9 reviewed?</p> <p>10 A. Well, it's my understanding</p> <p>11 that it is. Like any article that's</p> <p>12 published in the medical literature, there's</p> <p>13 usually some kind of reviewed process, where</p> <p>14 the editor receives it and asks a panel of</p> <p>15 experts to comment on it.</p> <p>16 Q. Okay. But this UpToDate</p> <p>17 information, that's not published in a</p> <p>18 medical journal, right?</p> <p>19 A. It's published online.</p> <p>20 Q. Right.</p> <p>21 A. As many medical literature now</p> <p>22 is published online, not in a hard journal.</p> <p>23 Q. Okay. But to be fair, you're</p> <p>24 not aware of whether or not the information</p>	<p style="text-align: right;">Page 36</p> <p>1 A. That's correct.</p> <p>2 Q. So as it relates to the</p> <p>3 opinions in your report, dated November 16,</p> <p>4 2018, the Saed manuscript that we've marked</p> <p>5 as Exhibit 4, did not inform those opinions;</p> <p>6 is that fair?</p> <p>7 A. That's correct.</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. I had an abstract that has some</p> <p>11 of this data that had been accepted to the</p> <p>12 SGO meeting for this year, but I did not have</p> <p>13 the entire report.</p> <p>14 BY MS. BROWN:</p> <p>15 Q. The next piece of information</p> <p>16 that counsel for plaintiffs provided, is a</p> <p>17 list of your invoices.</p> <p>18 (Deposition Exhibit 5 marked</p> <p>19 for identification.)</p> <p>20 BY MS. BROWN:</p> <p>21 Q. Did you type these invoices,</p> <p>22 Dr. Wolf?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. And so it looks like</p>
<p style="text-align: right;">Page 35</p> <p>1 you've provided as Exhibit 2 has gone through</p> <p>2 the formal peer-reviewed process, as we know</p> <p>3 it, as it relates to medical journals?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form, misstates her testimony.</p> <p>6 A. I don't understand -- I don't</p> <p>7 know the details of their peer review</p> <p>8 process.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. Fair enough. Counsel for the</p> <p>11 plaintiff also provided us with a manuscript,</p> <p>12 which we'll mark as Exhibit 4.</p> <p>13 (Deposition Exhibit 4 marked</p> <p>14 for identification.)</p> <p>15 BY MS. BROWN:</p> <p>16 Q. And this is a manuscript, one</p> <p>17 of the coauthors is Dr. Saed. Can you tell</p> <p>18 me, Doctor, when you reviewed the manuscript</p> <p>19 that we've marked as Exhibit 4?</p> <p>20 A. I received this manuscript and</p> <p>21 reviewed it on Friday, whatever date that</p> <p>22 was. I think the 4th of January.</p> <p>23 Q. And so this is something you</p> <p>24 have recently taken a look at; is that right?</p>	<p style="text-align: right;">Page 37</p> <p>1 there's actually a little different format</p> <p>2 between the first invoice, which appears to</p> <p>3 be January 2017, and later invoices; is that</p> <p>4 right?</p> <p>5 A. Can I see those, please?</p> <p>6 Q. Yeah, absolutely. I only have</p> <p>7 one copy, so we'll have to share.</p> <p>8 A. This is me. I typed this.</p> <p>9 Q. Okay.</p> <p>10 MS. O'DELL: We'll just say,</p> <p>11 for the record, the invoice in the</p> <p>12 form was done for purposes of my</p> <p>13 office paying it. So that's the</p> <p>14 format we use.</p> <p>15 But Dr. Wolf, you can explain</p> <p>16 how you conveyed your hours.</p> <p>17 A. Yes. I mean, this is how I</p> <p>18 sent them every time.</p> <p>19 BY MS. BROWN:</p> <p>20 Q. Okay.</p> <p>21 A. In an e-mail like this. I --</p> <p>22 this might be attached to my payment, but I</p> <p>23 hadn't really seen this form.</p> <p>24 Q. Okay. That's helpful. So a</p>

10 (Pages 34 to 37)

Judith K. Wolf, M.D.

Page 38	Page 40
<p>1 few follow-up questions, if I can grab that 2 back from you. As I understand it, Dr. Wolf, 3 the very first page of Exhibit 5, which is 4 entitled "Judith Wolf, Medical Expert Hours," 5 January 2017, at \$600 an hour, that's a 6 document you typed. Fair? 7 A. That's correct. 8 Q. Okay. And for each subsequent 9 invoice, you typed a document similar to the 10 first page of Exhibit 5. True? 11 A. Yes. 12 Q. Okay. And the remaining pages 13 of Exhibit 5 have sort of a -- a different 14 format. Would you agree? 15 A. The hours look the same, but -- 16 I mean the format of the hours look the same, 17 but the invoice at the top, no -- yes, that 18 looks different. 19 Q. Right. And I'm not trying to 20 be tricky, but you didn't type everything 21 after page 1 of Exhibit 5; is that fair? 22 MS. O'DELL: What I'm 23 conveying -- what I said. 24 MS. BROWN: Let's get an answer</p>	<p>1 invoices that Dr. Wolf sent to Beasley 2 Allen. For the record, what we have 3 are four additional pages of 4 Exhibit 5, which appear to be have 5 been generated by Beasley Allen. So 6 we'll request the underlying invoices 7 that came from the doctor. 8 MS. O'DELL: Fair enough. 9 MS. BROWN: Thank you. 10 MS. O'DELL: I would just note 11 for the record, just so there's no 12 suggestion otherwise, those are 13 contemporaneously provided. There's 14 no generation of that in conjunction 15 with this deposition. So I'm happy to 16 provide -- 17 MS. BROWN: And to be fair, I 18 don't mean to suggest anything 19 untoward. 20 MS. O'DELL: I want the record 21 to be clear. 22 MS. BROWN: As do we. 23 MS. O'DELL: So I will -- happy 24 to ask my office for the other</p>
Page 39	Page 41
<p>1 and then I'm happy to have you make 2 the statement for the record. I just 3 want an answer to that question. 4 MS. O'DELL: That's fair. You 5 can answer the question. 6 A. I didn't type the other ones. 7 MS. O'DELL: So the invoice was 8 prepared after the hours were 9 submitted to my office for purposes of 10 facilitating payment. So the data -- 11 to be clear, the data that was 12 provided was from Dr. Wolf. 13 MS. BROWN: Understood. 14 BY MS. BROWN: 15 Q. When you invoice the lawyers at 16 Beasley Allen, do you send a document that 17 looks like page 1 of Exhibit 5? 18 A. Yes. 19 Q. Okay. And have you done that 20 for every invoice that you've submitted 21 through your work on this matter? 22 A. Yes. 23 MS. BROWN: Okay. So I'm going 24 to request production of the original</p>	<p>1 documents. 2 MS. BROWN: Terrific. And so 3 we'll request the original invoices 4 that came from Dr. Wolf. 5 BY MS. BROWN: 6 Q. A couple of questions, 7 Doctor -- 8 MS. O'DELL: There weren't 9 invoices. Fair enough. You've made 10 your statement, but that's not what 11 they were. 12 MS. BROWN: We're on the same 13 page. 14 MS. O'DELL: Not maybe -- maybe 15 we're not. But anyway, we will -- I 16 will ask for whatever the list was 17 that was originally received. 18 BY MS. BROWN: 19 Q. Now, Dr. Wolf, the first 20 document we have in Exhibit 5, includes the 21 hours that you billed to Beasley Allen for 22 your work in January 2017. True? 23 A. Yes. 24 Q. And the very first entry that</p>

11 (Pages 38 to 41)

Judith K. Wolf, M.D.

Page 42	Page 44
<p>1 you have here is for a one and a half hour 2 meeting with Margaret Thompson. True? 3 A. Yes. 4 Q. Who is Margaret Thompson? 5 A. Margaret Thompson is one of the 6 attorneys for Beasley Allen. 7 Q. Okay. And how is it -- and 8 Ms. Thompson's here today; is that right? 9 A. Yes. She's sitting right 10 there. 11 Q. And how is it that you came to 12 meet Ms. Thompson? 13 A. So one of my neighbors, her 14 name is Ali Gallagher, lives in the same 15 building as I do. She is an attorney and 16 also a nurse practitioner by training. And I 17 met her at a social setting in the lobby of 18 my building. We have happy hours on Fridays. 19 And we sort of became friendly and talked and 20 then we became friends after that. She knows 21 what I do for a living. I'm a gynecologic 22 oncologist and take care of women with 23 ovarian cancer. 24 And one day we were talking</p>	<p>1 know. I know that they both have lived in 2 Austin for a long time. 3 BY MS. BROWN: 4 Q. When did this conversation take 5 place? 6 A. I don't remember. Sometime 7 before January of 2017, but I don't remember 8 the date. And it had to happen after 2015, 9 because I didn't meet her until then, so 10 sometime in that two-year period. 11 Q. Okay. And what did she tell 12 you about the question of talc and ovarian 13 cancer? 14 A. She was -- 15 MS. O'DELL: Are you referring 16 to Ms. Gallagher? 17 MS. BROWN: Yeah. Thank you. 18 BY MS. BROWN: 19 Q. I want to talk a little bit 20 about the conversation with Ms. Gallagher. 21 A. Yeah. 22 Q. As I understand it, this was 23 the first conversation you had regarding this 24 potential expert witness work; is that right?</p>
Page 43	Page 45
<p>1 about work, because she has a medical 2 background and lots of people ask me about 3 work, even if they don't. And we came about 4 talk -- she may have asked me, do I know 5 anything about talc and ovarian cancer, and I 6 said I was aware of articles about the risk 7 of talcum powder and ovarian cancer, and she 8 mentioned that she had a friend, a colleague, 9 who was working on a case. And I said I 10 would be interested in becoming more 11 involved, in learning more about it, so she 12 introduced us. 13 Q. To your knowledge, is 14 Ms. Gallagher an attorney at Beasley Allen? 15 A. To my knowledge, she is not. 16 Q. To your knowledge, is she a 17 plaintiffs' attorney? 18 A. To my knowledge, I don't really 19 know what kind of law she practices. 20 Q. Okay. And what is your 21 understanding of how Ms. Gallagher knows 22 Ms. Thompson? 23 MS. O'DELL: If you know. 24 A. You know what? I don't really</p>	<p>1 A. Yes. 2 Q. Okay. 3 A. So the conversation -- again, 4 the conversation happened more than two years 5 ago. My recollection was she asked me did I 6 know anything about the risk of ovarian 7 cancer in talcum powder use, and then we 8 started talking about it and I told her I 9 knew a little, I was aware of some 10 epidemiologic data suggesting it. And she 11 said she was asking because she had -- she 12 knew that there was some litigation about it. 13 And I said, one of my concerns with ovarian 14 cancer is there's very little we can do to 15 cure women. They present late, there's no 16 screening tests, the symptoms are nonspecific 17 and that if there's something that we can do 18 to prevent it, it would be helpful. And the 19 conversation went on and she asked me would I 20 be interested in talking to the people she 21 knew who were involved in the case, and I 22 said yes. 23 Q. And in 2015, where were you 24 working, Dr. Wolf?</p>

12 (Pages 42 to 45)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 46</p> <p>1 A. In 2015, I was working for a 2 diagnostic company called Vermillion, and I 3 was doing some clinical medicine as locum 4 tenens covering practices here and there, 5 just so I could keep my clinical skills up. 6 Q. And where were you doing your 7 clinical medicine during your time at 8 Vermillion? 9 A. At -- in Atlanta and in 10 Indianapolis. 11 Q. What facility in Atlanta? 12 A. Northwest Memorial, I believe 13 is the name of the hospital. 14 Q. And what was the other location 15 where you performed -- 16 A. Community Health in 17 Indianapolis. 18 Q. And so were you a physician on 19 staff at both of those locations? 20 A. On staff at the hospital, yes. 21 Q. And Vermillion, of course, was 22 aware of your clinical practice as well? 23 A. Yes. 24 Q. Okay. And how many patients</p>	<p style="text-align: right;">Page 48</p> <p>1 patients I treated. I would say that, in 2 general, my practice in the last five years 3 has been about a third ovarian cancer and 4 about 50 percent endometrial cancer. 5 Prior to 2014, when I was 6 practicing full time GYN oncology, more than 7 50 percent of my practice was ovarian cancer 8 because patients came from around the country 9 to see me, specifically with that issue. 10 Q. And that was during the time 11 period you were practicing at MD Anderson? 12 A. In Houston at MD Anderson and 13 at Banner health -- Banner MD Anderson in 14 Arizona. 15 Q. And as I understand, you left 16 MD Anderson to go to Vermillion, correct? 17 A. I left MD Anderson in Houston 18 to go to MD Anderson in Arizona. I left 19 Arizona to go to Vermillion. 20 Q. Okay. And then from Vermillion 21 you went to another start-up? 22 A. Provista Diagnostics, yes. 23 Q. Did you continue to treat 24 patients while you were at Provista?</p>
<p style="text-align: right;">Page 47</p> <p>1 would you say you were treating at that time? 2 A. You know, I was only 3 intermittently treating, so I can't really 4 give you a number. I don't know. 5 Q. Did you have set office hours 6 or hospital hours during that time period? 7 A. In Atlanta, I covered probably 8 three or four weeks a year when the doctors 9 were on vacation. In Indianapolis, when I 10 started, that's what I was doing. There was 11 one doctor and when he was gone, there was no 12 one to cover. 13 Q. Fair to say clinical medicine 14 was a small part of your practice during the 15 time period you were at Vermillion? 16 A. Yes. 17 Q. Did you treat any ovarian 18 cancer patients during the time period you 19 worked for Vermillion? 20 A. Yes. 21 Q. About how many patients would 22 you estimate you treated during that time 23 period? 24 A. I don't remember how many</p>	<p style="text-align: right;">Page 49</p> <p>1 A. I did. 2 Q. At the same two locations? 3 A. I don't believe I covered any 4 more in Atlanta, because the need was greater 5 in Indianapolis and, in fact, the last year 6 that I was working at Provista, I was 7 covering one week a month in Indiana. 8 Q. In what states are you licensed 9 to practice medicine? 10 A. My active licenses are in 11 Indiana, Georgia and Arizona. 12 Q. And you no longer have an 13 active license in Texas; is that right? 14 A. That's correct. 15 Q. Any other states that are no 16 longer active for you? 17 A. Minnesota. 18 Q. And then as I understand it, 19 you left Provista in about January of 2017? 20 A. No, I left Provista just -- my 21 official last day was October 1st of 2018. 22 Q. And so during part of the time 23 when you began your expert work for the 24 plaintiffs' lawyers in the talc litigation,</p>

Judith K. Wolf, M.D.

Page 50	Page 52
<p>1 you were working at Provista; is that right?</p> <p>2 A. That's correct.</p> <p>3 Q. Okay. Did you do any of</p> <p>4 work -- any expert work for plaintiffs'</p> <p>5 lawyers in the talc litigation while you were</p> <p>6 working at Vermillion?</p> <p>7 A. Let me think about that. Yes,</p> <p>8 I believe I did.</p> <p>9 Q. Did you disclose to Vermillion</p> <p>10 your work for plaintiffs' lawyers in the talc</p> <p>11 litigation?</p> <p>12 MS. O'DELL: If you did -- if</p> <p>13 you did any work during that time</p> <p>14 period.</p> <p>15 A. Yeah, I don't recall. I don't</p> <p>16 recall.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. Do you recall if Vermillion had</p> <p>19 a policy about its officials doing expert</p> <p>20 witness work?</p> <p>21 A. My recollection was that they</p> <p>22 did not have a policy.</p> <p>23 Q. And what were the circumstances</p> <p>24 that led to you leaving Provista in October</p>	<p>1 of your time would you say is devoted to</p> <p>2 treating patients at the Community Health</p> <p>3 Network?</p> <p>4 A. 60.</p> <p>5 MS. O'DELL: Just for</p> <p>6 clarification, are you asking for her</p> <p>7 time she's working at Community Health</p> <p>8 in Indianapolis, what percentage of</p> <p>9 her time is devoted to treating</p> <p>10 patients, or are you asking overall?</p> <p>11 It was just confusing.</p> <p>12 MS. BROWN: So the question --</p> <p>13 I'm looking at the real time. The</p> <p>14 question said, "devoted to treating</p> <p>15 patients at Community Health Network."</p> <p>16 MS. O'DELL: Okay. Thank you.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. Doctor, the final document that</p> <p>19 the lawyer for the plaintiffs, Ms. O'Dell</p> <p>20 gave me this morning, is -- we will mark as</p> <p>21 Exhibit 6, which appears to be an updated CV</p> <p>22 for you, dated January 4th, 2017.</p> <p>23 (Deposition Exhibit 6 marked</p> <p>24 for identification.)</p>
Page 51	Page 53
<p>1 of 2018?</p> <p>2 A. Provista? I could see that the</p> <p>3 company was having trouble getting funding,</p> <p>4 and, in fact, on October 1st, 2018, the</p> <p>5 company shut down. And so I had already been</p> <p>6 looking and I knew that Indiana wanted me to</p> <p>7 come there, so...</p> <p>8 Q. So when you say "the company</p> <p>9 shut down," what do you mean by that?</p> <p>10 A. They dissolved.</p> <p>11 Q. Was there any investigation</p> <p>12 into the company that led to the dissolution?</p> <p>13 A. No, it was just -- ran out of</p> <p>14 money, couldn't find new investors.</p> <p>15 Q. And since October of 2018,</p> <p>16 you've been working at the Indiana --</p> <p>17 Indianapolis location?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. What's the name of that?</p> <p>20 A. Community Health Network.</p> <p>21 Q. And you're a physician there</p> <p>22 part-time; is that right?</p> <p>23 A. That's correct.</p> <p>24 Q. And how many -- what percentage</p>	<p>1 BY MS. BROWN:</p> <p>2 Q. Do you have a copy in front of</p> <p>3 you?</p> <p>4 A. Yes, I do.</p> <p>5 Q. So the copy that was attached</p> <p>6 to your report, I believe was dated 2016.</p> <p>7 A. Yes.</p> <p>8 Q. Now, why would that be?</p> <p>9 A. Because from the time I started</p> <p>10 working with a company actually, I haven't</p> <p>11 had an assistant to help me update it and I'm</p> <p>12 not -- I haven't been good at keeping it</p> <p>13 updated.</p> <p>14 Q. Well, here's what I'm trying to</p> <p>15 understand. We got Exhibit 6, which is dated</p> <p>16 January of 2017, correct?</p> <p>17 A. Oh, it should be 2018. That's</p> <p>18 my -- see, I'm not a good typist.</p> <p>19 Q. Okay. So the correct date of</p> <p>20 Exhibit 6 is really January 4th, 2018?</p> <p>21 A. That's correct.</p> <p>22 MS. O'DELL: Should it be 2019?</p> <p>23 A. '19. '19.</p> <p>24</p>

14 (Pages 50 to 53)

Judith K. Wolf, M.D.

Page 54	Page 56
<p>1 BY MS. BROWN:</p> <p>2 Q. Okay. I think we're all on the</p> <p>3 same page now. All right. And you've</p> <p>4 updated this with additional employment that</p> <p>5 you've had --</p> <p>6 A. Yes.</p> <p>7 Q. -- since the time of your</p> <p>8 last --</p> <p>9 A. And a few publications that</p> <p>10 weren't on there.</p> <p>11 Q. Have you ever -- just to speak</p> <p>12 generally about your resumé, Doctor, have you</p> <p>13 ever published any peer-reviewed article</p> <p>14 regarding talcum powder and ovarian cancer?</p> <p>15 A. No.</p> <p>16 Q. Have you ever given any</p> <p>17 presentation regarding talcum powder and</p> <p>18 ovarian cancer?</p> <p>19 A. No.</p> <p>20 Q. Have you ever been invited to</p> <p>21 speak at any conference that dealt with</p> <p>22 issues regarding talcum powder and ovarian</p> <p>23 cancer?</p> <p>24 A. No.</p>	<p>1 A. In the popular press, I have</p> <p>2 talked about the use of birth control pills</p> <p>3 to reduce the risk of ovarian cancer, I've</p> <p>4 talked about the symptoms of ovarian cancer,</p> <p>5 I've talked about some of my research and</p> <p>6 treatment of ovarian cancer. I don't recall</p> <p>7 that I specifically talked about the risk of</p> <p>8 ovarian cancer.</p> <p>9 Q. Do you recall -- have you ever</p> <p>10 spoken -- have you ever gone on any -- strike</p> <p>11 that.</p> <p>12 Have you ever done any news</p> <p>13 interviews in which you have indicated your</p> <p>14 opinion in this case, which is that you</p> <p>15 believe that talc -- talcum powder causes</p> <p>16 ovarian cancer?</p> <p>17 A. I have not. But until I</p> <p>18 started reviewing all the literature for this</p> <p>19 case, I was generally aware of some</p> <p>20 epidemiologic studies, but I wasn't as</p> <p>21 convinced after reviewing the entire body of</p> <p>22 literature that I was able to review, that</p> <p>23 talcum powder causes ovarian cancer in some</p> <p>24 women and puts all women who use it at risk</p>
Page 55	Page 57
<p>1 Q. I've seen over the years,</p> <p>2 Doctor, you've done some popular press and</p> <p>3 news segments; is that right?</p> <p>4 A. Yes.</p> <p>5 Q. Have you ever given any news</p> <p>6 interviews regarding talcum powder and</p> <p>7 ovarian cancer?</p> <p>8 A. No.</p> <p>9 Q. You have, however, been an</p> <p>10 advocate for women's health issues over the</p> <p>11 years, correct?</p> <p>12 A. Yes.</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. And you've given a number of</p> <p>17 issues -- a number of interviews regarding</p> <p>18 ovarian cancer; is that fair?</p> <p>19 A. Yes.</p> <p>20 Q. Including the causes of ovarian</p> <p>21 cancer. True?</p> <p>22 A. In the popular -- are you</p> <p>23 asking me about in the popular press?</p> <p>24 Q. Uh-huh.</p>	<p>1 for ovarian cancer.</p> <p>2 Q. Prior to being hired as an</p> <p>3 expert witness for plaintiff lawyers in the</p> <p>4 talcum powder litigation, you, Dr. Wolf, were</p> <p>5 not as convinced that talcum powder causes</p> <p>6 ovarian cancer. True?</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form, misstates her testimony.</p> <p>9 A. Prior to being hired, I hadn't</p> <p>10 reviewed all the literature to be able to</p> <p>11 formulate my opinion.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. Prior to being hired by</p> <p>14 plaintiffs' lawyers in the talcum powder</p> <p>15 litigation, you did not hold the opinion that</p> <p>16 talcum powder causes ovarian cancer, correct?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 A. Prior to reviewing all the</p> <p>20 literature for this case, I wasn't aware of</p> <p>21 all the literature. I would say that I was</p> <p>22 aware that there was some indication that</p> <p>23 talcum powder increased the risk of ovarian</p> <p>24 cancer. What I was always told when I</p>

15 (Pages 54 to 57)

<p style="text-align: right;">Page 58</p> <p>1 brought that up was that, not to worry, 2 talcum powder doesn't contain asbestos 3 anymore and so that data is old and it 4 doesn't matter. 5 After reviewing all the 6 literature and the information that I have 7 seen, I don't believe that's true anymore. 8 BY MS. BROWN: 9 Q. You have formed the opinion 10 that talcum powder causes ovarian cancer 11 since being hired by the plaintiffs' lawyers 12 in the talcum powder litigation, correct? 13 MS. O'DELL: Object to the 14 form. 15 A. I want to think about how I 16 want to answer that, because the question is 17 a little confusing to me because I believe 18 what I said was, until I was aware of all of 19 the literature and looked at it as a whole, 20 all of the evidence, I hadn't formed the 21 opinion that talcum powder causes ovarian 22 cancer. I knew there was data that suggests 23 that talcum powder product increases the risk 24 of ovarian cancer and once I had all the</p>	<p style="text-align: right;">Page 60</p> <p>1 A. Twenty-four years. 2 Q. And for the 24 years that you 3 practiced as a gynecologic oncologist prior 4 to being hired by the plaintiffs' lawyers, it 5 was not your regular practice to ask your 6 patients if they used talcum powder. True? 7 MS. O'DELL: Object to the 8 form. 9 A. Prior to reviewing all the 10 literature and becoming convinced that it was 11 a concern, it was not my regular practice. 12 BY MS. BROWN: 13 Q. And you keep answering the 14 question by saying "prior to reviewing all 15 the literature." You reviewed all of the 16 literature at the request of the plaintiffs' 17 lawyers, correct? 18 MS. O'DELL: Object to the 19 form, asked and answered. 20 A. I reviewed all the literature 21 when I got -- when I wanted to learn more 22 about it, to become involved with deciding on 23 my own, whether this was something that I 24 should be concerned about. And if I reviewed</p>
<p style="text-align: right;">Page 59</p> <p>1 information, I fully believe it. And now I 2 tell all my patients, whether they have 3 ovarian cancer or not, not to use it or to 4 stop using it if they are. I tell all my 5 friends and family the same thing. 6 BY MS. BROWN: 7 Q. Prior to reviewing all of the 8 literature regarding talcum powder and 9 ovarian cancer, it was not your practice, as 10 a gynecologic oncologist, to tell your 11 patients not to use talcum powder. True? 12 A. Prior to reviewing all the 13 literature, it was not my practice to tell 14 patients, but I believe that I was naive, and 15 that when I take care of patients that come 16 to me that have cancer or they think they 17 have cancer, this was not something that I 18 focused on because I wasn't spending my time 19 reviewing all the literature. 20 Q. You practiced, Doctor, as a 21 gynecologic oncologist in a number of 22 different institutions for nearly 30 years 23 before being hired by plaintiffs' lawyers; is 24 that true?</p>	<p style="text-align: right;">Page 61</p> <p>1 the literature and felt there was no concern, 2 I would have a different opinion. 3 BY MS. BROWN: 4 Q. You reviewed all of the 5 literature regarding talcum powder and 6 ovarian cancer at the request of the 7 plaintiffs' lawyers, correct? 8 A. You're asking me at the 9 "request," and I -- that's the word that I'm 10 not -- I don't recall that being asked, but 11 the question at hand was, does talcum powder 12 cause ovarian cancer? 13 Q. I think I understand the 14 disconnect. You reviewed all of the 15 literature regarding talcum powder and 16 ovarian cancer in connection with your work 17 to answer a question that the plaintiffs' 18 lawyers asked you; is that fair? 19 A. In connection with this work, I 20 reviewed all of the literature. 21 Q. Okay. So if we wanted to date 22 the time at which you formed the opinion that 23 talcum powder causes ovarian cancer, it would 24 be after the time that you were hired by the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 62</p> <p>1 plaintiffs' lawyers, correct?</p> <p>2 A. I would say the date that I was</p> <p>3 convinced that talcum powder products cause</p> <p>4 ovarian cancer was after I reviewed all the</p> <p>5 literature. Prior to that, I knew that there</p> <p>6 was some papers that suggested there was a</p> <p>7 risk, but I didn't review all the literature</p> <p>8 to formulate an opinion about it.</p> <p>9 Q. And the reason that you</p> <p>10 formulated an opinion by reviewing all of the</p> <p>11 literature, was because you had been hired as</p> <p>12 an expert witness by plaintiffs' lawyers.</p> <p>13 True?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. I'm confused with the question.</p> <p>17 Because --</p> <p>18 BY MS. BROWN:</p> <p>19 Q. Well, let me see if I can</p> <p>20 orient you, Dr. Wolf. Here's what we're</p> <p>21 trying to understand. I understand your</p> <p>22 testimony was that for about 24 years as a</p> <p>23 practicing gynecologic oncologist, the</p> <p>24 potential association between talcum powder</p>	<p style="text-align: right;">Page 64</p> <p>1 health publications and went on TV shows,</p> <p>2 like Dr. Oz. True?</p> <p>3 A. Yes.</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 BY MS. BROWN:</p> <p>7 Q. And during those 24 years, you</p> <p>8 did not publish, write or speak about the</p> <p>9 opinion that talcum powder causes ovarian</p> <p>10 cancer, correct?</p> <p>11 A. What I published was my</p> <p>12 research, which was not on talcum powder</p> <p>13 products and ovarian cancer. What I spoke</p> <p>14 about was what I was asked to speak about,</p> <p>15 which was not talcum powder and ovarian</p> <p>16 cancer. When I was on the public -- when I</p> <p>17 was on the television or in the news, there</p> <p>18 was specific questions that I was being asked</p> <p>19 to speak about. They were not talcum powder</p> <p>20 and ovarian cancer.</p> <p>21 Q. But to be fair, some of the</p> <p>22 questions you were asked about is, what</p> <p>23 increases a woman's risk for ovarian cancer,</p> <p>24 right?</p>
<p style="text-align: right;">Page 63</p> <p>1 and ovarian cancer was not something you</p> <p>2 were, quote, focused on; is that right?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. It's not something that I was</p> <p>6 researching.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Okay. Nonetheless, you worked</p> <p>9 as an advocate for women's health during</p> <p>10 those 24 years. True?</p> <p>11 A. Most of those years.</p> <p>12 Q. You published a number of</p> <p>13 papers in the area of women's health,</p> <p>14 correct?</p> <p>15 A. Yes.</p> <p>16 Q. You were invited to a number of</p> <p>17 conferences and seminars and symposia on</p> <p>18 issues regarding ovarian cancer and women's</p> <p>19 health. True?</p> <p>20 A. Yes.</p> <p>21 Q. You published chapters in</p> <p>22 textbooks regarding ovarian cancer. True?</p> <p>23 A. Yes.</p> <p>24 Q. You gave interviews to women's</p>	<p style="text-align: right;">Page 65</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I don't remember the questions</p> <p>4 that I was asked about on Dr. Oz. I know</p> <p>5 that the purpose for me to go on that was to</p> <p>6 talk about the reduction in the risk of</p> <p>7 ovarian cancer by using birth control pills</p> <p>8 and I don't remember all of the questions.</p> <p>9 As far as I can recall, the other times I was</p> <p>10 on the news, that was not a question that was</p> <p>11 raised.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. When is the first date you can</p> <p>14 recall forming the opinion that you've</p> <p>15 provided in your expert report in the MDL?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form. Are you moving off going</p> <p>18 through the -- sort of the notice and</p> <p>19 the documents requested? I'm not --</p> <p>20 MS. BROWN: Shortly. You</p> <p>21 almost ready for a break?</p> <p>22 MS. O'DELL: Well, probably in</p> <p>23 the next five minutes or so, but what</p> <p>24 I was going to say and I neglected to</p>

17 (Pages 62 to 65)

Judith K. Wolf, M.D.

Page 66	Page 68
<p>1 say earlier is, there were certain</p> <p>2 documents that were requested through</p> <p>3 the notice. And just for the record,</p> <p>4 I wanted to state that plaintiffs</p> <p>5 served objections to certain of those</p> <p>6 requests and we produced documents</p> <p>7 here consistent with those objections.</p> <p>8 MS. BROWN: Right. We're in</p> <p>9 receipt of your objections.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. So Doctor, what -- let's mark</p> <p>12 your report as Exhibit 7.</p> <p>13 (Deposition Exhibit 7 marked</p> <p>14 for identification.)</p> <p>15 BY MS. BROWN:</p> <p>16 Q. And my question for you is</p> <p>17 that -- when's the first date by which you</p> <p>18 formed the opinions that are contained in</p> <p>19 this report that we've marked as Exhibit 7?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. I cannot recall the first date.</p> <p>23 BY MS. BROWN:</p> <p>24 Q. Okay. At the time that you</p>	<p>1 Is there anything else that</p> <p>2 you've brought with you today in response to</p> <p>3 our requests contained in Exhibit 1?</p> <p>4 MS. O'DELL: Other than the</p> <p>5 notebooks she's brought for her</p> <p>6 reference materials?</p> <p>7 A. No, I haven't -- I brought</p> <p>8 this -- it has my report and my reference</p> <p>9 list and my CV. These are all my references</p> <p>10 and all of that is contributing material.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Okay. So for the record, let's</p> <p>13 identify what you've just pointed out to us.</p> <p>14 You have a small binder in front of you --</p> <p>15 A. Yeah.</p> <p>16 Q. -- which appears to be tabbed.</p> <p>17 Did you do that tabbing?</p> <p>18 A. I did. And it just sort of</p> <p>19 says which section is which in my report.</p> <p>20 Q. Do you have any notes in your</p> <p>21 report, other than the tabs?</p> <p>22 A. No.</p> <p>23 Q. Okay. And what else is</p> <p>24 contained in that binder?</p>
Page 67	Page 69
<p>1 were approached by Ms. Gallagher in 2005, you</p> <p>2 did not hold the opinion that talcum powder</p> <p>3 causes ovarian cancer, correct?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. I didn't meet Ms. Gallagher</p> <p>7 till 2015.</p> <p>8 BY MS. BROWN:</p> <p>9 Q. Correct. I misspoke. I'm</p> <p>10 sorry.</p> <p>11 A. And the question was, I did not</p> <p>12 hold the opinion that -- I had concerns about</p> <p>13 talcum powder uses in ovarian cancer and I</p> <p>14 had enough concerns that I was interested</p> <p>15 enough to become involved in learning more</p> <p>16 about it.</p> <p>17 Q. To close the loop, then,</p> <p>18 Doctor, on the requests we made in the</p> <p>19 deposition notice that we've marked as</p> <p>20 Exhibit 1, we've marked a number of documents</p> <p>21 that lawyers for the plaintiffs produced</p> <p>22 early this morning. We're aware of the</p> <p>23 objections that lawyers for the plaintiffs</p> <p>24 have made.</p>	<p>1 A. My CV and then this is a list</p> <p>2 of all of the contributing material.</p> <p>3 Q. And then you have next to you</p> <p>4 three larger binders, which I think you said</p> <p>5 contain the references in the report; is that</p> <p>6 right?</p> <p>7 A. The references and also the</p> <p>8 other articles that you were provided, the</p> <p>9 new are in these and then that's all the</p> <p>10 contributing material.</p> <p>11 Q. Okay. And so for the record,</p> <p>12 behind you there's probably another ten or 12</p> <p>13 binders that you're suggesting contain the</p> <p>14 documents contained in -- listed in Exhibit B</p> <p>15 to your report?</p> <p>16 A. That's correct.</p> <p>17 Q. Okay. You didn't type Exhibit</p> <p>18 B to your report, did you, Doctor?</p> <p>19 A. I did not type it.</p> <p>20 Q. Do you know where Exhibit B to</p> <p>21 your report came from?</p> <p>22 A. The attorneys typed it up for</p> <p>23 me from all of my reference -- contributing</p> <p>24 material.</p>

18 (Pages 66 to 69)

Judith K. Wolf, M.D.

Page 70	Page 72
<p>1 Q. Okay. Did the attorneys 2 provide you with all of the materials that 3 are listed on Exhibit B? 4 A. No. 5 Q. Which of the materials on 6 Exhibit B were provided by the attorneys? 7 A. I can't tell you. It's a mix 8 of what I provided them, what they provided 9 me, what I asked them to provide to me. 10 Q. Well, let's start by 11 understanding the difference between your 12 reference list on page 18 of your report and 13 then Exhibit B to your report. Can you 14 explain to me the difference there? 15 A. The reference lists are 16 articles that I actually reference in my 17 report. And this is all the articles that 18 I -- or pieces of information that I 19 considered when drafting my report. 20 Q. Did you consider every piece of 21 information that's listed on the 28-page 22 Exhibit B? 23 A. Yes. 24 Q. Did you read every entry on the</p>	<p>1 A. No. 2 Q. Did you take any notes when you 3 were reviewing any of the materials cited in 4 your report? 5 A. I didn't take separate notes. 6 What I did was, I started writing things down 7 and used that as the draft of my report and 8 then just updated it every time I read more, 9 changed more, added, subtracted to it. 10 Q. Take a look, if you would, at 11 page 13 of Exhibit B. There are a number of 12 entries that begin with the letters J&J. Do 13 you see that? 14 A. I do. 15 Q. What are those? 16 A. Those are internal documents 17 from J&J that were provided to me from the 18 plaintiffs' attorneys. 19 Q. And did you request internal 20 documents be provided to you from the 21 plaintiffs' lawyers? 22 A. Some of them I might have 23 requested and some of them were provided to 24 me. But I can't tell you which is which by</p>
Page 71	Page 73
<p>1 28-page Exhibit B? 2 A. I did not read every word of 3 every entry. Some of them I looked at a 4 piece of it, if it was a reference from 5 something else that I wanted to confirm. 6 Some of it I looked at and set aside, didn't 7 feel like it was added -- additive or 8 pertinent to what I was reviewing. And -- 9 but these are all of the things that I looked 10 at in some way. 11 Q. How did you maintain all of the 12 documents contained at Exhibit B? And by 13 that I mean, do you have all of these 14 documents electronically or do you have a 15 hard copy at your house or office? 16 A. Both. 17 Q. Okay. You have a -- hard 18 copies of every document contained on Exhibit 19 B? 20 A. Yes. 21 Q. Okay. So you have 12 binders 22 in hard copy? 23 A. Yes. 24 Q. Do they have notes on them?</p>	<p>1 looking at that list. 2 Q. In the normal course of your 3 practice as a gynecologic oncologist, do you 4 review internal company documents in making 5 medical decisions? 6 A. I don't have access to them. 7 MS. O'DELL: Object to the 8 form. 9 BY MS. BROWN: 10 Q. So as part of your work as a 11 treating physician, you don't rely on 12 internal company documents. Fair? 13 MS. O'DELL: Object to the 14 form. 15 A. I don't have access to internal 16 company documents. 17 BY MS. BROWN: 18 Q. So you don't rely on them, 19 right? 20 MS. O'DELL: Object to the 21 form. 22 A. Well, I don't have access to 23 them. 24</p>

Judith K. Wolf, M.D.

Page 74	Page 76
<p>1 BY MS. BROWN: 2 Q. Do you have any -- so that 3 means you haven't used them in your practice 4 as a gynecologic oncologist, right? 5 MS. O'DELL: Object to the 6 form. 7 A. Not that I recall. 8 BY MS. BROWN: 9 Q. And the 20-some-odd J&J 10 documents you have listed here at Exhibit 13, 11 do you have any idea what percentage of the 12 entire document production from J&J these 20 13 documents comprise? 14 A. Of all of J&J's internal 15 documents? I don't. 16 Q. Was it important to you, to 17 consider the context of all of the internal 18 documents you have cited at Exhibit 13? 19 MS. O'DELL: Object to the 20 form. 21 A. Say that again. 22 BY MS. BROWN: 23 Q. Was it important to you -- 24 first of all, did you request that the</p>	<p>1 Q. I want to know -- sitting here 2 today, it's my opportunity to understand what 3 forms the basis of your opinions and I want 4 know if there's information in an internal 5 Johnson & Johnson document that forms the 6 basis of your opinion that talc causes 7 ovarian cancer. 8 MS. O'DELL: Objection, asked 9 and answered. 10 A. My opinion is not based on any 11 one single document or any one single source 12 of documents. It's the whole of the 13 documents that I reviewed. 14 BY MS. BROWN: 15 Q. So what information do you rely 16 on from the whole of the 20 J&J documents you 17 looked at? 18 MS. O'DELL: Objection, 19 mischaracterizes the witness's 20 testimony. 21 A. So I'm going to say that this 22 is my contributing materials list. It's not 23 even -- none of the -- those internal 24 documents are referenced in my -- in my</p>
Page 75	Page 77
<p>1 lawyers give you some of these internal 2 documents? 3 A. I don't recall specifically if 4 I requested these or they gave them to me. I 5 just don't recall. 6 Q. Do internal J&J documents form 7 the basis of your opinions in this 8 litigation? 9 MS. O'DELL: Object to the 10 form. 11 A. The basis of my opinion is the 12 review of everything that I looked at in 13 total, not -- there isn't any one thing that 14 forms the basis of my opinion. It's the 15 whole of the evidence. 16 BY MS. BROWN: 17 Q. Okay. So identify for me what 18 information in the internal Johnson & Johnson 19 documents you're relying on to form your 20 opinion. 21 A. Well, these are in my 22 contributing data lists, not in my reference 23 lists. So I'd have to look at all of them 24 to --</p>	<p>1 opinion. So I don't know how else to answer 2 to you, other than to say I looked at all of 3 the evidence. The things that I felt were 4 important, I referenced in my opinion. I 5 don't recall what's in all of those. 6 BY MS. BROWN: 7 Q. So there are internal company 8 documents listed on page 13 of Exhibit B, the 9 contents of which, sitting here today, you're 10 unaware of; is that fair? 11 MS. O'DELL: Object. That 12 misstates her testimony. 13 A. What I -- 14 MS. O'DELL: Excuse me. Object 15 to the form of the question. 16 You may answer. 17 A. What I said is, I can't recall 18 what those individually are, sitting here 19 today. I could look at them if you'd like me 20 to. 21 BY MS. BROWN: 22 Q. Well, I want you to do that if 23 it forms the basis of your opinion. If it 24 doesn't and it's just something that was</p>

20 (Pages 74 to 77)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 78</p> <p>1 given to you by the plaintiffs' lawyers, we 2 can move on. But if there's something in the 3 20 documents that the plaintiffs' lawyers 4 have listed on page 13 of Exhibit B to your 5 report that forms the basis of your opinion, 6 I want to know what that is. 7 MS. O'DELL: Objection to the 8 form, asked and answered three times 9 now. 10 A. The basis of my opinion is not 11 formed by any one document. 12 BY MS. BROWN: 13 Q. Is the basis of your opinion 14 formed, in part, by internal Johnson 15 & Johnson documents? 16 MS. O'DELL: Object to the 17 form. 18 A. I would have to look at all of 19 those documents again to tell you if there 20 was something specifically in there and what 21 the -- I just -- they're numbers to me. 22 Looking at them here, I don't recall that -- 23 what's in each one of those to tell you if 24 there's something specifically that formed my</p>	<p style="text-align: right;">Page 80</p> <p>1 form. I think Dr. Wolf stated 2 previously they were provided to her 3 because they weren't available 4 elsewhere. 5 MS. BROWN: Well, I need her to 6 say that, though. I need that 7 testimony from her. 8 BY MS. BROWN: 9 Q. Dr. Wolf, did you -- were the 10 J&J documents on page 13 provided to you by 11 plaintiffs' lawyers? 12 MS. O'DELL: Object to the 13 form. 14 A. The documents were provided to 15 me by plaintiffs' lawyers. 16 BY MS. BROWN: 17 Q. And are you -- can you provide 18 us with an understanding of the methodology 19 the plaintiffs' lawyers employed in terms of 20 which documents to select for your review? 21 MS. O'DELL: Object to the 22 form, asked and answered. 23 A. I'm not sure what you're 24 asking.</p>
<p style="text-align: right;">Page 79</p> <p>1 opinion. 2 MS. O'DELL: And you're 3 referring to page 13. 4 THE WITNESS: Of Exhibit B. 5 MS. O'DELL: Of Exhibit B. 6 We've been going about an hour and ten 7 minutes. 8 BY MS. BROWN: 9 Q. Sure. I'll just finish real 10 quick on the company documents. If you just 11 look at page 12 of your report, you list a 12 number -- sorry, Exhibit B to your report, 13 you list a number of Imerys entries. Do you 14 see that there? 15 A. I do. 16 Q. Who is Imerys? 17 A. Imerys is a mining company. 18 Q. Did you select these internal 19 Imerys documents to review? 20 A. These were provided to me. 21 Q. And same with the J&J document, 22 did you select those to review or were they 23 provided to you? 24 MS. O'DELL: Objection to the</p>	<p style="text-align: right;">Page 81</p> <p>1 BY MS. BROWN: 2 Q. Do you have an understanding of 3 how the plaintiffs' lawyers went about 4 picking the 20 J&J documents and the 15 5 Imerys documents that appear on Exhibit B to 6 your report? 7 MS. O'DELL: Object to the 8 form. 9 A. I didn't specifically ask them 10 how they came about finding them, looking for 11 them, if that's what you're asking me. 12 BY MS. BROWN: 13 Q. Do you have any understanding, 14 sitting here today, of how the internal 15 documents listed on page B of your report, 16 were compiled for your review? 17 MS. O'DELL: Object to the 18 form, asked and answered. 19 A. I'm not aware of how the 20 plaintiffs' attorneys compiled the report. I 21 didn't ask them their methodology. 22 BY MS. BROWN: 23 Q. Having reviewed the internal 24 documents that the plaintiffs' lawyers gave</p>

21 (Pages 78 to 81)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 82</p> <p>1 you, did you ask them for additional internal 2 documents? 3 A. I don't recall. 4 Q. Did you ask the plaintiffs' 5 lawyers any questions about any of the 6 internal documents they provided you? 7 MS. O'DELL: Excuse me, I'm 8 going to object to that question. 9 MS. BROWN: I'll rephrase. 10 MS. O'DELL: You're not 11 entitled to understand -- 12 MS. BROWN: I'll rephrase -- 13 (Simultaneous discussion 14 interrupted by reporter.) 15 MS. O'DELL: Let me finish my 16 objection before you interrupt me. 17 MS. BROWN: Sure. 18 MS. O'DELL: So she's not 19 entitled to ask you questions about 20 your conversations with counsel. 21 MS. BROWN: That's not entirely 22 true. 23 BY MS. BROWN: 24 Q. I'm certainly entitled to know</p>	<p style="text-align: right;">Page 84</p> <p>1 MS. O'DELL: Fair enough. 2 MS. BROWN: If she asked you, 3 as lawyers for the plaintiffs, for any 4 information on which she is relying 5 for her opinion, then that's 6 discoverable. And so my question -- I 7 appreciate your work-product concern. 8 My question is meant to stay within 9 the bounds of the Federal Rules, which 10 is that -- was there any information 11 that you provided her about these 12 documents on which she is relying to 13 form her opinion. That's 14 discoverable. 15 MS. O'DELL: That's not the 16 question you asked her. 17 MS. BROWN: Yes, absolutely. 18 MS. O'DELL: You asked if she 19 asked any questions, which goes to 20 communication. And what the rule 21 allows discovery on are the materials 22 provided to Dr. Wolf, which are 23 available here for your review. 24 They're available from the list that</p>
<p style="text-align: right;">Page 83</p> <p>1 about information that counsel provided to 2 you that you're relying on to form your 3 opinions. So I will rephrase the question to 4 ask just for whether you asked for any -- you 5 have any questions about these internal 6 documents that you asked of plaintiffs that 7 you are relying on for your opinions here? 8 MS. O'DELL: Dr. Wolf, I'm 9 going to instruct you not to discuss 10 conversations you had with counsel. 11 You're certainly entitled, 12 under the rules, to know what 13 materials were provided for Dr. Wolf, 14 which we are doing that, but you're 15 not entitled to understand any 16 conversations that occurred between 17 Dr. Wolf and counsel. I'm going to 18 instruct the witness not to answer. 19 MS. BROWN: But that's not the 20 law. So the law is -- 21 MS. O'DELL: The law is -- 22 MS. BROWN: Let me finish. I 23 let you put your statement on the 24 record. Let me just finish.</p>	<p style="text-align: right;">Page 85</p> <p>1 you've been provided. You're not 2 entitled to any discussions, and that 3 was what the question focused on. So 4 why don't we -- 5 MS. BROWN: We are entitled -- 6 I just want to finish this question 7 and we'll absolutely take a break. We 8 are entitled to any information, 9 verbal or otherwise that you may have 10 given her, if she's relying on it. 11 And so I will rephrase the question to 12 make clear, that all I want to know is 13 if she asked the lawyers a question 14 about the documents, the answer to 15 which she relies on for her opinion. 16 That is 100 percent discoverable. 17 MS. O'DELL: It is not. That's 18 a communication between counsel and 19 she's not going to testify. Now, all 20 the materials that she's relying on 21 are present in the -- excuse me. 22 They're present before Dr. Wolf and on 23 the table beside Dr. Wolf. Those are 24 the materials she's relying on and</p>

22 (Pages 82 to 85)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 86</p> <p>1 you're welcome to ask all of the</p> <p>2 questions you'd like. But in terms of</p> <p>3 communications between counsel and</p> <p>4 Dr. Wolf, you're not entitled to</p> <p>5 discover that and I'm going to</p> <p>6 instruct the witness not to answer.</p> <p>7 MS. BROWN: Here's what we need</p> <p>8 to do so we can take it to the judge.</p> <p>9 I need an answer to the question, is</p> <p>10 she relying on information from the</p> <p>11 lawyers regarding the documents. I</p> <p>12 need -- that's a yes or no. That's</p> <p>13 not even questionable. If she says</p> <p>14 yes and you instruct her not to</p> <p>15 answer, we'll take it to the judge.</p> <p>16 We need an answer to that straight up.</p> <p>17 MS. O'DELL: So I want to make</p> <p>18 sure I understand. Are you asking her</p> <p>19 if she relies on these materials?</p> <p>20 MS. BROWN: No. Here's where</p> <p>21 we are. I want to know if she asked</p> <p>22 the lawyers a question about the</p> <p>23 documents, she got an answer and she's</p> <p>24 relying on that answer to form the</p>	<p style="text-align: right;">Page 88</p> <p>1 missing each other, so let me ask my</p> <p>2 question and you instruct.</p> <p>3 MS. O'DELL: I don't think we</p> <p>4 are.</p> <p>5 MS. BROWN: We'll have it on</p> <p>6 the record and be able to take it up.</p> <p>7 For the record, my position is, any</p> <p>8 information from counsel or otherwise,</p> <p>9 on which the witness relies for her</p> <p>10 opinion is plainly discoverable under</p> <p>11 the Federal Rules.</p> <p>12 MS. O'DELL: Disagree with that</p> <p>13 position.</p> <p>14 BY MS. BROWN:</p> <p>15 Q. Dr. Wolf, one quick question</p> <p>16 here, and then we'll certainly take a break.</p> <p>17 I know we've been going a while.</p> <p>18 Did counsel for the plaintiffs</p> <p>19 provide you with any information regarding</p> <p>20 internal company documents on which you are</p> <p>21 relying to form the basis of your opinions in</p> <p>22 this lawsuit?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 question. And answer the question to</p>
<p style="text-align: right;">Page 87</p> <p>1 basis of her opinion, and that is</p> <p>2 discoverable under the Federal Rules.</p> <p>3 So we're going to start with that</p> <p>4 question, did you rely on something</p> <p>5 the lawyers told you about the</p> <p>6 documents, and then if you want to</p> <p>7 instruct from there, we'll tee it up</p> <p>8 and talk to the judge about it because</p> <p>9 that's discoverable.</p> <p>10 MS. O'DELL: I think the issue</p> <p>11 is the discussion about "rely." And</p> <p>12 what -- but you're asking her about</p> <p>13 discussions with counsel. And that's</p> <p>14 different. And so she's not going to</p> <p>15 testify about discussions with</p> <p>16 counsel. The materials that she</p> <p>17 considered and she relied on are</p> <p>18 present in front of her and to her</p> <p>19 side.</p> <p>20 MS. BROWN: Let me --</p> <p>21 MS. O'DELL: That's what's</p> <p>22 discoverable and that's where we're</p> <p>23 going to stay.</p> <p>24 MS. BROWN: Okay. We're</p>	<p style="text-align: right;">Page 89</p> <p>1 the degree you understand it. If you</p> <p>2 don't understand the question, you</p> <p>3 don't have to answer it, Dr. Wolf.</p> <p>4 A. My understanding of the</p> <p>5 question, what I hear you asking me, is did I</p> <p>6 ask counsel questions about this, information</p> <p>7 I got from them, not from the documents but</p> <p>8 from the answer to my question, did I use</p> <p>9 that information to form my opinion? The</p> <p>10 answer to that is no.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Thank you, Dr. Wolf.</p> <p>13 MS. BROWN: Why don't we go</p> <p>14 ahead and take a break.</p> <p>15 MS. O'DELL: Okay.</p> <p>16 MS. BROWN: Thank you.</p> <p>17 THE VIDEOGRAPHER: Going off</p> <p>18 the record. The time is 10:21 a.m.</p> <p>19 (Recess taken from 10:21 a.m.</p> <p>20 to 10:33 a.m.)</p> <p>21 THE VIDEOGRAPHER: Back on the</p> <p>22 record. The time is 10:33 a.m.</p> <p>23 BY MS. BROWN:</p> <p>24 Q. Welcome back, Dr. Wolf.</p>

23 (Pages 86 to 89)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 90</p> <p>1 A. Thank you.</p> <p>2 Q. Dr. Wolf, counsel for the</p> <p>3 plaintiffs indicated to me earlier this</p> <p>4 morning, that there are some additional</p> <p>5 documents that you have reviewed since the</p> <p>6 time of your report. That would include the</p> <p>7 pending health Canada risk assessment; is</p> <p>8 that correct?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. When did you review</p> <p>11 that?</p> <p>12 A. Sometime within the last few</p> <p>13 weeks. I don't remember the exact date.</p> <p>14 Q. Counsel indicated that you've</p> <p>15 reviewed an article with the lead author</p> <p>16 Taher, T-a-h-e-r; is that correct?</p> <p>17 A. That's correct.</p> <p>18 Q. When did you review that?</p> <p>19 A. Around the same time as the</p> <p>20 Canadian health assessment.</p> <p>21 Q. Were both the health Canada</p> <p>22 proposed report and the Taher article</p> <p>23 provided to you by counsel for the</p> <p>24 plaintiffs?</p>	<p style="text-align: right;">Page 92</p> <p>1 A. I don't have the supplemental</p> <p>2 materials. I just have the Taher somewhere.</p> <p>3 MS. BROWN: Counsel, has that</p> <p>4 material been provided to the doctor?</p> <p>5 MS. O'DELL: Yes.</p> <p>6 MS. BROWN: Okay. We'll</p> <p>7 request production of the supplemental</p> <p>8 materials as referenced in the Taher</p> <p>9 report.</p> <p>10 MS. O'DELL: Let me make sure.</p> <p>11 What do you mean "supplemental"? Let</p> <p>12 me make sure I understand what you're</p> <p>13 saying. She's provided the Taher and</p> <p>14 the -- she's provided the Taher paper</p> <p>15 and the causal assessment.</p> <p>16 MS. BROWN: Okay. The Taher</p> <p>17 paper makes references in numerous</p> <p>18 places to supplemental materials, and</p> <p>19 my question was whether you've</p> <p>20 provided those supplemental materials</p> <p>21 to the witness and if so, I'll request</p> <p>22 production of it.</p> <p>23 MS. O'DELL: Okay. Let me</p> <p>24 check that.</p>
<p style="text-align: right;">Page 91</p> <p>1 A. Yes.</p> <p>2 Q. Do you know if the Taher</p> <p>3 article is publicly available yet?</p> <p>4 A. I don't know. The copy that I</p> <p>5 have says that it's submitted for publication</p> <p>6 or is going to be submitted for publication.</p> <p>7 I haven't done a search to see if it's</p> <p>8 publicly available yet.</p> <p>9 Q. Have -- did you note in your</p> <p>10 review of the Taher article, that it</p> <p>11 references, in numerous places, supplemental</p> <p>12 materials?</p> <p>13 A. Yes.</p> <p>14 Q. Have you reviewed the</p> <p>15 supplemental materials on which Taher relies?</p> <p>16 A. I haven't reviewed them all.</p> <p>17 Some of them I had reviewed otherwise, but</p> <p>18 I -- I haven't reviewed them all, no.</p> <p>19 Q. Did plaintiffs' lawyers give</p> <p>20 you access to the supplemental materials</p> <p>21 relied on in Taher?</p> <p>22 A. I don't know.</p> <p>23 Q. Do you have those materials</p> <p>24 with you here today?</p>	<p style="text-align: right;">Page 93</p> <p>1 MS. BROWN: Okay. Thank you.</p> <p>2 BY MS. BROWN:</p> <p>3 Q. For your purposes, though,</p> <p>4 Dr. Wolf, it's not something you have on hand</p> <p>5 sitting here today?</p> <p>6 A. It's not.</p> <p>7 Q. And because these materials</p> <p>8 were recently provided to you by counsel for</p> <p>9 the plaintiffs, they did not form the basis</p> <p>10 of the report that you authored, dated</p> <p>11 November 16th, 2018; is that fair?</p> <p>12 A. That's fair.</p> <p>13 Q. Okay. Counsel indicated you</p> <p>14 have seen some of the other expert reports</p> <p>15 from witnesses for plaintiffs' lawyers in</p> <p>16 this litigation; is that right?</p> <p>17 A. That's correct.</p> <p>18 Q. Okay. Can you tell me which</p> <p>19 ones you've reviewed?</p> <p>20 A. Can I see the list of all of</p> <p>21 them? I don't --</p> <p>22 MS. O'DELL: I don't have a</p> <p>23 list.</p> <p>24 A. I reviewed some of the</p>

24 (Pages 90 to 93)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 94</p> <p>1 epidemiology ones, but I don't remember the 2 names. I reviewed part of one of the other 3 GYN oncology ones. It seemed to be similar 4 to mine. I don't read it all. I didn't read 5 the third. I can't remember. 6 BY MS. BROWN: 7 Q. Okay. So let's back up. How 8 many -- I assume the reports of these other 9 experts were provided to you from the 10 plaintiffs' lawyers; is that right? 11 A. That's correct. 12 Q. Okay. When did you -- did you 13 receive them all at once? 14 A. I did. 15 Q. And do you recall approximately 16 when you received them? 17 A. I don't know. Sometime after 18 the reports were all submitted. I don't 19 remember the date. 20 Q. Okay. Prior to issuing your 21 report, dated November 16th, 2018, did you 22 see any other expert reports? 23 MS. O'DELL: Object to the 24 form.</p>	<p style="text-align: right;">Page 96</p> <p>1 for the plaintiffs submitted reports like 2 yours from a number of different people, 3 right? 4 A. Yes. 5 Q. And there came a point in time 6 when the plaintiffs' lawyers sent you some of 7 those reports, correct? 8 A. Yes. 9 Q. Did they send you completed 10 reports or did they send you draft reports? 11 A. They sent me the completed 12 reports that had already been submitted and 13 turned in. I didn't see any drafts of 14 anybody else's reports. 15 Q. Got it. So in writing your 16 report in this case, which we have marked as 17 Exhibit 7 and which is dated November 16th, 18 2018, you did not rely on the opinions of 19 another expert. Fair? 20 MS. O'DELL: Object to the 21 form. 22 A. My understanding what you're 23 asking me is, did I rely on the opinions of 24 the expert reports in this case? No, I had</p>
<p style="text-align: right;">Page 95</p> <p>1 A. I didn't see any of the expert 2 reports for this case. 3 BY MS. BROWN: 4 Q. Okay. In -- fair to say, then, 5 the opinions that you have contained in your 6 report, dated November 16, 2018, you're not 7 relying on any other plaintiff expert in 8 forming these opinions; is that right? 9 MS. O'DELL: Object to the 10 form. Other than cited in her actual 11 report. 12 MS. BROWN: Counsel, it's 13 objection to form. Don't testify for 14 her. 15 A. Well, the Plunkett deposition, 16 I believe, is a reference in my report. 17 BY MS. BROWN: 18 Q. Well, it couldn't be a 19 reference in your report because it didn't 20 happen till after your report, right? 21 A. Sorry. Yes. 22 Q. Okay. So we're going to get to 23 Plunkett. Let's keep that to the side. What 24 I'm interested -- you understand that lawyers</p>	<p style="text-align: right;">Page 97</p> <p>1 not seen them. 2 BY MS. BROWN: 3 Q. That was exactly what I was 4 asking. Did you type the report that we've 5 marked as Exhibit 7 yourself, Doctor? 6 A. You mean my fingers on? 7 Q. Correct. 8 A. I typed some of the drafts. 9 The final report, I dictated most of it. 10 Q. So to whom did you dictate the 11 report? 12 A. I don't remember her name. 13 Someone who works with the plaintiffs' 14 attorneys. I'm not a typist. 15 Q. Fair enough. How many hours 16 did you spend preparing the report that we've 17 marked as Exhibit 7? 18 MS. O'DELL: Object to the 19 form. 20 A. An estimate of how much time, I 21 would say 20 to 30 hours, total. I mean, 22 there were several drafts and then even when 23 I thought it was a final draft, a few tweaks 24 and revisions here and there. And I still</p>

25 (Pages 94 to 97)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 98</p> <p>1 see some typos and errors that if I had it</p> <p>2 back, I would fix and change.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. Did someone other than you</p> <p>5 write some of the information contained in</p> <p>6 Exhibit 7?</p> <p>7 A. Exhibit 7 is my report?</p> <p>8 Q. Correct.</p> <p>9 A. Other than things that I have</p> <p>10 in quotes that I've pulled from articles, no</p> <p>11 one else wrote it.</p> <p>12 Q. Other than information that you</p> <p>13 have in quotes, it's your testimony that all</p> <p>14 of the language that we see in Exhibit 7 is</p> <p>15 your own; is that right?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. I wrote the report, the entire</p> <p>19 report.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. Do you know who Dr. Blair Smith</p> <p>22 is?</p> <p>23 A. Dr. Blair Smith?</p> <p>24 Q. Correct.</p>	<p style="text-align: right;">Page 100</p> <p>1 A. Yes.</p> <p>2 Q. You wrote that sentence?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. Skipping down to the</p> <p>5 paragraph below "Summary of Epidemiological</p> <p>6 Evidence," the paragraph that begins, "When</p> <p>7 looking at epidemiological studies in their</p> <p>8 totality" -- are you with me?</p> <p>9 A. Yes.</p> <p>10 Q. Did you write this entire</p> <p>11 paragraph here?</p> <p>12 A. Yes.</p> <p>13 Q. Did you give Dr. Ellen Blair</p> <p>14 Smith the authority to copy that into her</p> <p>15 report?</p> <p>16 A. I didn't speak with Dr. Ellen</p> <p>17 Blair Smith.</p> <p>18 Q. Are you surprised to learn that</p> <p>19 the information that you wrote on page 8 also</p> <p>20 appears in Dr. Blair Smith's report, which</p> <p>21 I'm handing you as Exhibit 8.</p> <p>22 (Deposition Exhibit 8 marked</p> <p>23 for identification.)</p> <p>24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 99</p> <p>1 A. Is that -- is that Ellen Blair</p> <p>2 Smith?</p> <p>3 Q. Correct.</p> <p>4 A. I do know her, yes.</p> <p>5 Q. Okay. Did you work with</p> <p>6 Dr. Blair Smith on your report?</p> <p>7 A. I did not.</p> <p>8 Q. Okay. Do you know why a</p> <p>9 paragraph in your report would be exactly the</p> <p>10 same as that contained in Dr. Smith -- Blair</p> <p>11 Smith's report?</p> <p>12 A. I don't.</p> <p>13 Q. Okay. Let's take a look at</p> <p>14 that. If you look at page 8 of your report,</p> <p>15 Doctor. Right above the bold text that says</p> <p>16 "Meta-Analysis," do you see that sentence?</p> <p>17 A. Uh-huh.</p> <p>18 Q. It says, "All of the cohort</p> <p>19 studies are limited by lack of power, failure</p> <p>20 to make the appropriate queries, selection</p> <p>21 bias and short follow-up."</p> <p>22 Do you see that?</p> <p>23 A. I do.</p> <p>24 Q. Are those your words?</p>	<p style="text-align: right;">Page 101</p> <p>1 form.</p> <p>2 A. Is it marked somewhere here</p> <p>3 what it is?</p> <p>4 BY MS. BROWN:</p> <p>5 Q. It is. If you look at page 16,</p> <p>6 Doctor. And I'll direct you to the -- one,</p> <p>7 two, three -- the end of the first -- go to</p> <p>8 the third complete paragraph that begins "In</p> <p>9 my opinion." You with me?</p> <p>10 A. Uh-huh.</p> <p>11 Q. Okay. And the end of that</p> <p>12 paragraph contains the very first sentence I</p> <p>13 asked you to read, right? "All of the cohort</p> <p>14 studies are limited by lack of power."</p> <p>15 Correct?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. What I can say when I look at</p> <p>19 these, she cited the same limitations as I</p> <p>20 did, and that's not that surprising to me.</p> <p>21 BY MS. BROWN:</p> <p>22 Q. Okay. And if you look at --</p> <p>23 when looking at the epidemiology studies, do</p> <p>24 you see that that paragraph is the same,</p>

26 (Pages 98 to 101)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 102</p> <p>1 Doctor?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form. Are you referring to when --</p> <p>4 the fourth -- the last paragraph above</p> <p>5 "Mechanism"?</p> <p>6 MS. BROWN: "When looking at</p> <p>7 epidemiological studies."</p> <p>8 BY MS. BROWN:</p> <p>9 Q. Do you see that, Doctor?</p> <p>10 A. Is that the last -- you're</p> <p>11 talking about the last paragraph?</p> <p>12 Q. Sorry, of your report. Page 8.</p> <p>13 Is that your language, Doctor?</p> <p>14 A. This is my language; this is</p> <p>15 her language. I see some words that are the</p> <p>16 same. The conclusions are similar, but --</p> <p>17 BY MS. BROWN:</p> <p>18 Q. And you see some sentences --</p> <p>19 MS. O'DELL: Excuse me. She's</p> <p>20 not finished.</p> <p>21 Would you like to finish,</p> <p>22 Dr. Wolf?</p> <p>23 A. But I mean, I'm just mostly</p> <p>24 looking at the length of it and it's not even</p>	<p style="text-align: right;">Page 104</p> <p>1 BY MS. BROWN:</p> <p>2 Q. In writing your report, Doctor,</p> <p>3 did you take any language from other</p> <p>4 articles?</p> <p>5 MS. O'DELL: Sorry, do you mean</p> <p>6 quote language?</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Did you -- is any of the</p> <p>9 language contained in your report not your</p> <p>10 own; meaning did it come from publicly</p> <p>11 available sources or articles?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. Quotes in my report came from</p> <p>15 articles.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. In writing your report, did you</p> <p>18 consult Wikipedia?</p> <p>19 A. Did I do what?</p> <p>20 Q. Did you consult Wikipedia?</p> <p>21 A. No.</p> <p>22 Q. Do you know what that is?</p> <p>23 A. I do, but I don't consult for</p> <p>24 any medical literature or scientific</p>
<p style="text-align: right;">Page 103</p> <p>1 the same length, so I don't see how it's the</p> <p>2 exact same thing.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. You see some sentences that are</p> <p>5 identical, right, Doctor?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. I don't see -- give me a chance</p> <p>9 to look at the entire thing.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Sure.</p> <p>12 A. Because I don't see -- I see</p> <p>13 one sentence is the same. "There appears to</p> <p>14 be no significant publication bias."</p> <p>15 Q. And also, Doctor, the sentence</p> <p>16 that we just talked about, "All of the cohort</p> <p>17 studies are limited by failure," that's the</p> <p>18 same, right?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. No, it's not the same. It</p> <p>22 raises the same points, but it's not the</p> <p>23 same.</p> <p>24</p>	<p style="text-align: right;">Page 105</p> <p>1 literature.</p> <p>2 Q. You don't consider Wikipedia to</p> <p>3 be a scientifically reliable source; is that</p> <p>4 right?</p> <p>5 A. I don't.</p> <p>6 Q. Okay. And in coming up with</p> <p>7 your report, that's not something that you</p> <p>8 cut and pasted from; is that right?</p> <p>9 A. I didn't look at Wikipedia to</p> <p>10 prepare my report.</p> <p>11 Q. And there aren't parts of your</p> <p>12 report that someone else did for you; is that</p> <p>13 right?</p> <p>14 MS. O'DELL: Object to form.</p> <p>15 A. That's right.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. On page 2 of your report,</p> <p>18 Doctor, you indicate the method -- you talk</p> <p>19 about the methodology you employed here. Do</p> <p>20 you see that?</p> <p>21 A. Yes.</p> <p>22 Q. Describe for us -- I understand</p> <p>23 you have it discussed in your report, but</p> <p>24 describe for us what methodology you employed</p>

27 (Pages 102 to 105)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 106</p> <p>1 to answer the question in this case.</p> <p>2 A. So that's -- this is why I</p> <p>3 provided the UpToDate evidence-based</p> <p>4 medicine. So I started with the question.</p> <p>5 The question is, does general use of talcum</p> <p>6 powder cause ovarian cancer. And then</p> <p>7 researched the literature, looking for human</p> <p>8 studies, animal studies, in vitro studies.</p> <p>9 And then evaluated the validity of the</p> <p>10 studies as a whole, by looking at their</p> <p>11 materials and methods, the results and</p> <p>12 conclusions that they drew, what journal</p> <p>13 the -- if it was published in a peer-reviewed</p> <p>14 journal, what journal it was in, what year it</p> <p>15 was published, were there multiple studies</p> <p>16 showing similar findings, were there</p> <p>17 outliers, and then from that formed my</p> <p>18 opinion.</p> <p>19 Q. And your conclusion is that</p> <p>20 genital talc use causes ovarian cancer,</p> <p>21 correct?</p> <p>22 A. That is -- genital talcum</p> <p>23 powder use, yes.</p> <p>24 Q. And is your opinion limited to</p>	<p style="text-align: right;">Page 108</p> <p>1 a woman is exposed to when she uses it</p> <p>2 perineally?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. Are you asking me if I've done</p> <p>6 a study? I'm not sure what you're asking.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. In forming your opinion in this</p> <p>9 case, that talcum powder causes ovarian</p> <p>10 cancer, have you attempted to quantify how</p> <p>11 much talcum powder causes ovarian cancer?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. In reviewing the articles, some</p> <p>15 of the studies have tried to look at length</p> <p>16 of time, frequency of use, years of use,</p> <p>17 total applications. It's hard for me to know</p> <p>18 what that amount is, because I don't know in</p> <p>19 each individual woman, like, how much she put</p> <p>20 in. And I also don't know in each individual</p> <p>21 woman, what her risk might be from the talc,</p> <p>22 based on her own genetic makeup and other</p> <p>23 things in her immune system and how she</p> <p>24 responds to it.</p>
<p style="text-align: right;">Page 107</p> <p>1 a certain quantity of genital powder use?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. It's not. And I had a hard</p> <p>5 time with that issue just because I don't</p> <p>6 know what a dose is, because how much do you</p> <p>7 shake, how much do you apply, it's hard to</p> <p>8 know a certain amount.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. In forming your opinions in</p> <p>11 this case, have you attempted to quantify how</p> <p>12 much talcum powder an individual woman would</p> <p>13 be exposed to when using it in the genital</p> <p>14 area?</p> <p>15 MS. O'DELL: Objection to the</p> <p>16 form. Dr. Wolf's being offered for</p> <p>17 general causation, not for a specific</p> <p>18 plaintiff.</p> <p>19 A. Repeat the question again.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. Sure. We were talking about</p> <p>22 how much powder use, in your opinion, causes</p> <p>23 ovarian cancer. And my question is, have you</p> <p>24 attempted to quantify how much talcum powder</p>	<p style="text-align: right;">Page 109</p> <p>1 BY MS. BROWN:</p> <p>2 Q. Have you calculated how much</p> <p>3 genital talc powder is needed to cause</p> <p>4 ovarian cancer?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. Again, I think that my -- it's</p> <p>8 difficult, even from reviewing the literature</p> <p>9 and from all the questions that were asked,</p> <p>10 queried, to know how much any woman is</p> <p>11 exposed to when she uses it.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. So what you're identifying is</p> <p>14 one of the limitations of the talc</p> <p>15 epidemiology, correct?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. What I'm identifying is one of</p> <p>19 the limitations of knowing what dose is safe.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. In your mind, is there a dose</p> <p>22 of genital talcum powder that does not cause</p> <p>23 ovarian cancer?</p> <p>24 A. I don't know.</p>

Judith K. Wolf, M.D.

Page 110	Page 112
<p>1 Q. Have you investigated whether</p> <p>2 or not there is an amount of talcum powder</p> <p>3 that can be used perineally without</p> <p>4 increasing the risk for ovarian cancer?</p> <p>5 MS. O'DELL: Objection, asked</p> <p>6 and answered.</p> <p>7 A. I don't know if there is an</p> <p>8 amount that's safe. I don't know how I could</p> <p>9 ethically test that. I'm not aware of</p> <p>10 anything in the literature that says, "This</p> <p>11 dose is safe, this dose is not." Because</p> <p>12 even in all of the studies, what is a dose?</p> <p>13 One shake? Two shakes? A hard shake? A</p> <p>14 light shake?</p> <p>15 BY MS. BROWN:</p> <p>16 Q. Is your opinion, Dr. Wolf, that</p> <p>17 some amount of perineal talcum powder use</p> <p>18 causes ovarian cancer, is that opinion</p> <p>19 dependent on an assumption that talcum powder</p> <p>20 is contaminated with asbestos?</p> <p>21 A. No, because --</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. -- talcum powder is a mix of</p>	<p>1 BY MS. BROWN:</p> <p>2 Q. Are you referring to</p> <p>3 plaintiffs' expert witness reports?</p> <p>4 A. Let me look in my report here</p> <p>5 for just one second. I'm sorry, I just need</p> <p>6 to look in here to find it. Because there is</p> <p>7 plaintiffs' expert witness, but --</p> <p>8 MS. O'DELL: Take your time,</p> <p>9 Doctor.</p> <p>10 THE WITNESS: All right.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. And, Doctor, maybe I can help.</p> <p>13 On page 9 of your report, you reference in</p> <p>14 the third paragraph --</p> <p>15 A. Yes.</p> <p>16 Q. -- that you believe Dr. Longo</p> <p>17 and Rigler have demonstrated talc to be --</p> <p>18 may be contaminated with asbestos. Do you</p> <p>19 see that?</p> <p>20 A. That's correct. And then also</p> <p>21 there's the deposition of John Hopkins.</p> <p>22 Q. What information are you</p> <p>23 relying on from the deposition of John</p> <p>24 Hopkins?</p>
Page 111	Page 113
<p>1 things, right? It's a mix of platy talc,</p> <p>2 fibrous talc, asbestos, heavy metals have</p> <p>3 been found in it, nickel and chromium and</p> <p>4 cobalt, and then all of the fragrances. And</p> <p>5 I have seen the expert report of Michael</p> <p>6 Crowley, where he assessed the irritant</p> <p>7 quality of some of the fragrances. And so</p> <p>8 when I look at the talcum powder product, I</p> <p>9 look at it as a whole.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Do you believe there is</p> <p>12 asbestos in talcum powder?</p> <p>13 A. I've seen evidence that there</p> <p>14 is asbestos found in at least 60 percent of</p> <p>15 talcum powder that's been evaluated that I've</p> <p>16 seen.</p> <p>17 Q. Is it your opinion in this</p> <p>18 case, that 60 percent of talcum powder is</p> <p>19 contaminated with asbestos?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form, asked and answered.</p> <p>22 A. In the reports that I've seen,</p> <p>23 60 percent of the time there was evidence of</p> <p>24 asbestos.</p>	<p>1 A. A report that I saw.</p> <p>2 Q. Okay. What -- you just pulled</p> <p>3 out a document from your binder. What is</p> <p>4 that, Doctor?</p> <p>5 A. That is the -- this is part of</p> <p>6 the deposition, right? Yeah. It's in my</p> <p>7 references.</p> <p>8 BY MS. BROWN:</p> <p>9 Q. Okay. Can I see it?</p> <p>10 A. Yeah. It was just printed</p> <p>11 separately so it can be bigger.</p> <p>12 Q. And what you have just handed</p> <p>13 me, Dr. Wolf, is -- it bears an exhibit</p> <p>14 sticker Hopkins 28, and do you know -- it</p> <p>15 appears to be a large printout of some kind</p> <p>16 of Excel chart. Do you know what this is?</p> <p>17 A. This was from his deposition of</p> <p>18 testing of talcum powder products.</p> <p>19 Q. Did you read the deposition of</p> <p>20 Dr. John Hopkins?</p> <p>21 A. I did not see the entire</p> <p>22 deposition.</p> <p>23 Q. Were you provided with the</p> <p>24 deposition?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 114</p> <p>1 A. If I was, I don't recall.</p> <p>2 Q. Did you ask to see Exhibit 28</p> <p>3 to John Hopkins' deposition?</p> <p>4 A. Specifically ask for that? I</p> <p>5 did not. I was provided it.</p> <p>6 Q. So the lawyers decided to give</p> <p>7 you John Hopkins' Exhibit 28; is that right?</p> <p>8 A. I received it from the lawyers.</p> <p>9 Q. Okay. And do you know what's</p> <p>10 contained within Exhibit 28?</p> <p>11 A. Do I know what's contained</p> <p>12 within it? It's a chart of testing of talcum</p> <p>13 powder from various sources and various time</p> <p>14 periods, how the test was done and what the</p> <p>15 results showed, as well as a few other things</p> <p>16 on there.</p> <p>17 Q. Did you -- do you know who</p> <p>18 created this chart, Dr. Wolf?</p> <p>19 A. I don't.</p> <p>20 Q. Do you have any idea if the</p> <p>21 four pages of testing contained in Exhibit 28</p> <p>22 to John Hopkins' deposition is representative</p> <p>23 of all the testing that was done on Johnson</p> <p>24 & Johnson's product?</p>	<p style="text-align: right;">Page 116</p> <p>1 BY MS. BROWN:</p> <p>2 Q. So in terms of interpreting the</p> <p>3 findings of the chart, which list a number of</p> <p>4 different test methods, you'd agree you're</p> <p>5 not a microscopist. True?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. Can you define what a</p> <p>9 "microscopist" is in your -- from what you're</p> <p>10 asking me?</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Sure. Are you -- do you hold</p> <p>13 yourself out to the medical community as an</p> <p>14 expert in light microscopy in looking --</p> <p>15 using various different types of microscopy</p> <p>16 to study minerals?</p> <p>17 A. No, I'm not.</p> <p>18 Q. And you understand that the</p> <p>19 chart you just handed me includes a number of</p> <p>20 different test methods, correct?</p> <p>21 A. Yes.</p> <p>22 Q. And you're not aware whether</p> <p>23 those test methods are even capable of</p> <p>24 distinguishing or finding asbestos, correct?</p>
<p style="text-align: right;">Page 115</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I don't know if it is or it</p> <p>4 isn't, but what I know is what I see there,</p> <p>5 is that the results show evidence of asbestos</p> <p>6 contamination over a period of time.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Do you know -- are you familiar</p> <p>9 with the test method "XRD"?</p> <p>10 A. I'm not a geologist and I don't</p> <p>11 understand the test methods. So I'm going to</p> <p>12 have to say I would defer to the geologist to</p> <p>13 answer a question about that.</p> <p>14 Q. So in terms of whether or not a</p> <p>15 test method known as "XRD" is even capable of</p> <p>16 distinguishing between asbestiform and</p> <p>17 nonasbestiform minerals, you would defer to</p> <p>18 somebody else on that question; is that</p> <p>19 right?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. What I'm going to say is that</p> <p>23 the details of how that's performed, I am not</p> <p>24 aware of.</p>	<p style="text-align: right;">Page 117</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I'm assuming since they found</p> <p>4 asbestos, that they are. I'm assuming that</p> <p>5 since they were used to try to identify</p> <p>6 asbestos, that they are.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Show me on this chart what</p> <p>9 asbestos finding you're referring to, Doctor.</p> <p>10 A. The second page, tremolite --</p> <p>11 here, tremolite, tremolite, actinolite</p> <p>12 fibrous talc, tremolite, tremolite,</p> <p>13 actinolite, tremolite, actinolite -- sorry.</p> <p>14 I'm sorry. I didn't mean to go so fast. I'm</p> <p>15 looking at what tests revealed.</p> <p>16 Q. And are you familiar, Doctor,</p> <p>17 with the fact that tremolite exists both as</p> <p>18 tremolite asbestos and as the nonasbestiform</p> <p>19 version of that mineral? Are you aware of</p> <p>20 that?</p> <p>21 A. Yes.</p> <p>22 Q. Okay. And do you -- what</p> <p>23 information are you relying on that the</p> <p>24 tremolite that's indicated in that chart is</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 118</p> <p>1 tremolite asbestos and not the nonasbestiform 2 version? 3 MS. O'DELL: Object to the 4 form. 5 A. I wasn't given that 6 information. All I can say is that there 7 is -- some of them say "tremolite," others 8 say "fibrous crocidolite, fibrous tremolite, 9 actinolite." 10 BY MS. BROWN: 11 Q. And whether the information 12 that's contained on the exhibit from 13 Dr. Hopkins' deposition that was given to you 14 by the plaintiffs' lawyers, whether that, in 15 fact, indicates a finding of asbestos, you're 16 not the expert in that. Fair? 17 MS. O'DELL: Object to the 18 form. 19 A. I'm looking at the results, and 20 even if I take out ones that just say 21 "tremolite," and don't tell me if it's the 22 asbestos form or not, I see -- I see others 23 that do say "asbestos, asbestos fibers, 24 fibrous talc" --</p>	<p style="text-align: right;">Page 120</p> <p>1 BY MS. BROWN: 2 Q. And have you reviewed -- what 3 you just pointed me to, Dr. Wolf, is a 4 testing from the 1970s by Dr. Langer, 5 correct? 6 A. Can I see the whole thing? 7 Q. Sure. You pointed me to 8 Dr. Langer, Mount Sinai, 1975, right? 9 A. Yes. 10 Q. Okay. Are you familiar with 11 Dr. Langer's testing of talcum powder 12 products in the 1970s? 13 MS. O'DELL: Object to the 14 form. And if you're going to ask 15 questions about the exhibit, if you'll 16 put it back in front of the witness. 17 MS. BROWN: Absolutely. 18 MS. O'DELL: You've asked a 19 question, she's going to respond, so 20 hand her back Exhibit 28. 21 MS. BROWN: I'm not sure she 22 needs it to answer it. 23 MS. O'DELL: I'm sure counsel 24 has a copy of Exhibit 28 if you -- if</p>
<p style="text-align: right;">Page 119</p> <p>1 BY MS. BROWN: 2 Q. Show me where it says 3 "asbestos." 4 A. This one says "confirmed 5 asbestos." 6 Q. And did you ask -- did you look 7 at the product that was being tested here, 8 Doctor? Meaning, do you even know if this 9 was cosmetic talcum powder? 10 MS. O'DELL: Object to the 11 form. If you want her to look at the 12 exhibit in full, you can ask a 13 question. 14 BY MS. BROWN: 15 Q. Sure. You just pointed me to a 16 line on the chart that says they're testing 17 ore mud. Do you have any source of 18 information that would lead you to believe 19 that that was ore that was used to make 20 cosmetic talc? 21 MS. O'DELL: Object to the 22 form. 23 A. Are you talking about the one 24 below it that says --</p>	<p style="text-align: right;">Page 121</p> <p>1 you need it. I'm sure you have it 2 committed to memory. 3 A. Can you ask the question again? 4 BY MS. BROWN: 5 Q. Sure. In supporting your view 6 that 60 percent of talcum powder products are 7 contaminated with asbestos, you've handed me 8 a chart that the lawyers gave you from 9 Dr. Hopkins' deposition and pointed me to an 10 entry of a test that Dr. Langer performed in 11 the 1970s, right? 12 MS. O'DELL: Object to the 13 form, misstates her testimony as to 14 the percentage. It's not what she 15 referred to. 16 A. That's the line I pointed at. 17 BY MS. BROWN: 18 Q. Okay. But to be fair, 19 Dr. Wolf, you are not familiar with the 20 testing that Dr. Langer did on talcum powder 21 products in the 1970s, right? 22 A. I am not. 23 Q. Okay. And you are certainly 24 not aware of the work that the Food and Drug</p>

Judith K. Wolf, M.D.

Page 122	Page 124
<p>1 Administration did to check all of the work 2 that Dr. Langer did, correct? 3 MS. O'DELL: Object to the 4 form. 5 A. I am not aware of all of the 6 testing or checking that the FDA did to test 7 Dr. Langer's work. 8 BY MS. BROWN: 9 Q. And so in giving that 10 testimony, you were not aware that the FDA 11 tested that Dr. Langer sample and determined 12 there was no asbestos? 13 A. That specific -- 14 MS. O'DELL: Excuse me. 15 BY MS. BROWN: 16 Q. Let me just -- 17 MS. O'DELL: No. I get to -- 18 BY MS. BROWN: 19 Q. I need to ask my question. 20 MS. O'DELL: I need to have the 21 opportunity to object. If you'd give 22 me just a moment. Object to the form 23 of the question. Misstates the 24 record.</p>	<p>1 Q. Did you review the testing that 2 the FDA did of Johnson's Baby Powder in the 3 1970s? 4 MS. O'DELL: Object to the 5 form. 6 A. I don't recall reviewing in 7 detail the testing that they did. 8 BY MS. BROWN: 9 Q. Were you aware that the FDA 10 determined, based on its own testing of 11 Johnson's baby powder product in the 1970s, 12 that it was asbestos free? 13 MS. O'DELL: Object to the 14 form. 15 A. I was aware that they reported 16 that. 17 BY MS. BROWN: 18 Q. Did you consider the finding of 19 the United States Food and Drug 20 Administration's own testing of baby powder's 21 product, before coming to your opinion that 22 60 percent of baby powder is contaminated 23 with asbestos? 24 MS. O'DELL: Object to the</p>
Page 123	Page 125
<p>1 MS. BROWN: But here's what 2 happened. I didn't get the question 3 out. 4 MS. O'DELL: Yes, you did. 5 MS. BROWN: So let me get the 6 question on the record -- 7 MS. O'DELL: Yes, you did. 8 MS. BROWN: -- and then we'll 9 leave time for Ms. O'Dell to object 10 and then, Doctor, you can answer. 11 So my question was, you're not 12 aware that the FDA tested all of the 13 Langer samples that were conducted in 14 the 1970s and determined that J&J's 15 product was free from asbestos, right? 16 MS. O'DELL: Object to the 17 form, misstates the record. 18 A. I'm not aware that the FDA 19 tested all of Dr. Langer's testing, no. 20 BY MS. BROWN: 21 Q. Were you aware that the FDA 22 tested Johnson & Johnson's baby powder in the 23 1970s at all? 24 A. Yes.</p>	<p>1 form. 2 A. What I said, I believe, was 3 that what I saw of the samples that I saw 4 tested, 60 percent showed evidence. I'm not 5 saying that -- I didn't say that -- what I 6 said was, of what I saw, 60 percent showed 7 evidence of asbestos. 8 BY MS. BROWN: 9 Q. And you're getting that 60 10 percent figure from an expert report for a 11 plaintiffs' lawyer in litigation, correct? 12 MS. O'DELL: Object to the 13 form. 14 A. Are you referring to the Longo 15 and Rigler report? 16 BY MS. BROWN: 17 Q. I am. 18 A. Yes. 19 Q. Okay. So the basis for your 20 opinion that 60 percent of baby powder 21 products are contaminated with asbestos is a 22 plaintiffs' expert report in litigation. 23 True? 24 MS. O'DELL: Object to the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 126</p> <p>1 form.</p> <p>2 A. My -- 60 percent of what I saw</p> <p>3 tested had evidence.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. So the entire basis of your</p> <p>6 opinion that 60 percent of what was tested</p> <p>7 had asbestos comes from this Longo report,</p> <p>8 right?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. 60 percent of what I saw.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. What methodology did you employ</p> <p>14 in terms of weighting the evidence from</p> <p>15 Dr. Longo, a plaintiffs' expert witness, or</p> <p>16 the Food and Drug Administration?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 A. I will have to say I took them</p> <p>20 both into consideration. Given that there's</p> <p>21 been a continued concern since the 1970s and</p> <p>22 beyond, that there is a relationship with</p> <p>23 general talcum powder use and ovarian cancer,</p> <p>24 I had to look at all of the information. And</p>	<p style="text-align: right;">Page 128</p> <p>1 tested baby powder in 2009 and 2010?</p> <p>2 A. I don't recall.</p> <p>3 Q. Is it important to you, to have</p> <p>4 considered that information before offering</p> <p>5 an expert opinion that baby powder's</p> <p>6 contaminated with asbestos?</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form.</p> <p>9 A. Can you show me that</p> <p>10 information?</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Sure.</p> <p>13 THE WITNESS: Can you pull up</p> <p>14 the Longo report for me?</p> <p>15 (Deposition Exhibit 9 marked</p> <p>16 for identification.)</p> <p>17 BY MS. BROWN:</p> <p>18 Q. I'm marking, Dr. Wolf, as</p> <p>19 Exhibit 9 to your deposition, a printout from</p> <p>20 the FDA's website regarding talc, and this,</p> <p>21 I'll represent to you, is a report from the</p> <p>22 FDA's testing of baby powder products for</p> <p>23 asbestos in 2009-2010. Certainly take as</p> <p>24 long as you need to review it, but I'd refer</p>
<p style="text-align: right;">Page 127</p> <p>1 if there is any asbestos in baby powder, it's</p> <p>2 one of the components that could be</p> <p>3 carcinogenic.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. Okay. We're talking about the</p> <p>6 basis for your opinion to believe there is</p> <p>7 asbestos in baby powder. Are you with me?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. Yes.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Okay. And I understand one of</p> <p>13 the things you relied on was Dr. Longo's</p> <p>14 report, right?</p> <p>15 A. Yes.</p> <p>16 Q. And you are testifying that you</p> <p>17 also took into consideration the FDA's</p> <p>18 testing in the 1970s, correct?</p> <p>19 A. Yes.</p> <p>20 Q. Did you consider the FDA's</p> <p>21 testing in 2009 and 2010?</p> <p>22 A. I'd have to look at that</p> <p>23 information.</p> <p>24 Q. Did you know that the FDA</p>	<p style="text-align: right;">Page 129</p> <p>1 you to the very last page, which tests the</p> <p>2 Johnson's baby powder product and reports, by</p> <p>3 both PLM and TEM, no asbestos.</p> <p>4 MS. O'DELL: Would you -- would</p> <p>5 you mind -- is it 9? Exhibit 9?</p> <p>6 MS. BROWN: Yes. Sorry,</p> <p>7 Exhibit 9. Sorry.</p> <p>8 MS. O'DELL: And feel free to</p> <p>9 take an opportunity to review</p> <p>10 Exhibit 9, Dr. Wolf.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Dr. Wolf, I see you're looking</p> <p>13 at the Longo report, which I'm going to give</p> <p>14 you plenty of time to look at, but I just</p> <p>15 want to ask you a question about Exhibit 9,</p> <p>16 the FDA's testing.</p> <p>17 A. And what is your question?</p> <p>18 Q. Were you aware of the FDA's</p> <p>19 testing of Johnson's baby powder products in</p> <p>20 2009 and 2010?</p> <p>21 A. I can't recall specifically</p> <p>22 that I was aware of that. Am I surprised</p> <p>23 that they tested? I'm not.</p> <p>24 Q. Right. So what -- did you</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 130</p> <p>1 consider third-party testing of Johnson's 2 baby powder, like Princeton, MIT, Colorado 3 School of Mines? Did you consider any of 4 those testings? 5 MS. O'DELL: Object to the 6 form. 7 A. Well, some of those were on 8 this report. 9 BY MS. BROWN: 10 Q. Did you consider the testing 11 that they did in connection with the 1970s 12 Langer findings that determined there was no 13 asbestos in Johnson's baby powder? 14 MS. O'DELL: Object to the 15 form, misstates the record. 16 A. I'm getting a little confused 17 about what you're asking, about "the 18 consider." I mean, I considered everything 19 that I saw. 20 BY MS. BROWN: 21 Q. And that's what I'm trying to 22 find out. So I understand you are here today 23 giving us an opinion that baby powder 24 contains asbestos. True?</p>	<p style="text-align: right;">Page 132</p> <p>1 A. Yes. As well as the Hopkins 2 data. 3 BY MS. BROWN: 4 Q. But we talked about -- 5 MS. O'DELL: Excuse me. 6 Dr. Wolf, when you say the "Hopkins 7 data," are you referring to the 8 Exhibit 28? 9 THE WITNESS: Yes. 10 BY MS. BROWN: 11 Q. We talked about Exhibit 28, 12 Doctor, and admittedly you're not able to 13 interpret the testing methods that were used 14 there, correct? 15 MS. O'DELL: Object to the 16 commentary. It's not what she said. 17 It misrepresents her testimony. 18 A. You asked me about -- 19 MS. BROWN: Hold on. 20 BY MS. BROWN: 21 Q. Your counsel thinks I'm 22 misrepresenting your testimony and I 23 certainly don't mean to do that. We agreed, 24 Doctor, did we not, that you're not a</p>
<p style="text-align: right;">Page 131</p> <p>1 A. Some baby powder, I believe, 2 contains asbestos, yes. 3 Q. What percentage of baby powder 4 contains asbestos? 5 A. It doesn't matter what 6 percentage to me, if any of it does. I'm 7 telling you the reports that I've seen, 60 8 percent in the testing that I've seen. I 9 don't care if that's -- if you took all baby 10 powder and it's 60 percent or not. If 11 there's any in there, it's a concern to me. 12 Q. Okay. So I understand you to 13 have an opinion there is asbestos in some 14 amount of baby powder, correct? 15 MS. O'DELL: Object to the 16 form. 17 A. In the testing that I've seen, 18 yes, I believe there's asbestos in some baby 19 powder. 20 BY MS. BROWN: 21 Q. Okay. And you're talking about 22 Dr. Longo's litigation testing, right? 23 MS. O'DELL: Object to the 24 form.</p>	<p style="text-align: right;">Page 133</p> <p>1 microscopist? 2 MS. O'DELL: Object to the 3 form. 4 A. See, when you say 5 "microscopist," I say that that -- that's a 6 term to me that means more than I think 7 you're meaning to say. I routinely look at 8 light microscopy, a pathology of gynecologic 9 cancers. So in that area, would you say I'm 10 a microscopist? I don't know. Do I 11 routinely look for asbestos? I do not. 12 BY MS. BROWN: 13 Q. Right. You don't hold yourself 14 out to the medical community as someone who 15 is qualified to look at bulk samples of baby 16 powder for the presence of asbestos. True? 17 A. I do not. 18 Q. You have never used a 19 transmission electron microscope. True? 20 A. I might have used one when I 21 was in medical school or a fellowship. 22 Q. It's not a regular part of your 23 practice to use TEM or SEM electron 24 microscopes. True?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 134</p> <p>1 A. It's not.</p> <p>2 Q. Okay. We're going to have to</p> <p>3 change the tape in a few minutes, but you</p> <p>4 hold the opinion, do you not, Doctor, that</p> <p>5 baby powder is contaminated with asbestos?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form, asked and answered.</p> <p>8 A. I believe that some baby powder</p> <p>9 contains asbestos.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Do you believe that to be true</p> <p>12 in terms of current baby powder on the shelf?</p> <p>13 A. The testing that I've seen goes</p> <p>14 up through the 1990s. So that's all I can</p> <p>15 speak to.</p> <p>16 Q. Okay. You're not offering an</p> <p>17 opinion that any baby powder after the 1990s</p> <p>18 contains asbestos; is that right?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. I'm not offering any opinion</p> <p>22 about what's in baby powder tests beyond</p> <p>23 where I've seen testing of it.</p> <p>24</p>	<p style="text-align: right;">Page 136</p> <p>1 you're asking me? I don't know -- I don't</p> <p>2 have that information.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. Have you reviewed Dr. Longo's</p> <p>5 report on the samples he acquired, in part,</p> <p>6 from eBay?</p> <p>7 A. I'm laughing at eBay.</p> <p>8 Q. I know. It sounds funny,</p> <p>9 doesn't it?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. I believe there was some</p> <p>13 commercial -- commercial products. I didn't</p> <p>14 know it was eBay. But commercial product</p> <p>15 that was off the shelf.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. Did you review and are you</p> <p>18 relying on Dr. Longo's report of vintage baby</p> <p>19 powder bottles that he purchased on eBay?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. I'm just looking for his</p> <p>23 sources.</p> <p>24 (Witness reviews document.)</p>
<p style="text-align: right;">Page 135</p> <p>1 BY MS. BROWN:</p> <p>2 Q. And the testing that you've</p> <p>3 seen is in the form of Dr. Longo's report.</p> <p>4 True?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. Where did Dr. Longo get</p> <p>7 the samples that he tested; do you know?</p> <p>8 A. I thought that some of them --</p> <p>9 I'll have to look here again. From J&J.</p> <p>10 Q. Did you review, Doctor -- and</p> <p>11 when you say "J&J," do you mean the samples</p> <p>12 that came through warehouses and were</p> <p>13 archived in the J&J "museum"?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form, misstates the record.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. Well, that's a good point.</p> <p>18 MS. O'DELL: Testify to what</p> <p>19 you've seen, Doctor.</p> <p>20 A. What I see is the source of the</p> <p>21 talcum powder for these J&J historical</p> <p>22 samples came from Italian Vermont talc mines.</p> <p>23 So they were J&J historical powder samples.</p> <p>24 Where they were stored at J&J -- is that what</p>	<p style="text-align: right;">Page 137</p> <p>1 A. When I looked in this report</p> <p>2 for where -- the materials and methods, I</p> <p>3 don't see anything about eBay on here.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. Did the lawyers for plaintiffs</p> <p>6 give you Dr. Longo's prior reports?</p> <p>7 A. Yes, they're here somewhere.</p> <p>8 BY MS. BROWN:</p> <p>9 Q. And I don't mean to have you</p> <p>10 have to do homework here, Dr. Wolf. I just</p> <p>11 want to know if you're relying on Dr. Longo's</p> <p>12 testing of the eBay samples.</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. I'm relying on whole -- the</p> <p>16 whole of Dr. Longo's testing.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. Okay. And explain to us how</p> <p>19 you employed your methodology of the weight</p> <p>20 of the evidence to evaluate Dr. Longo's</p> <p>21 findings, the FDA's findings, third-party</p> <p>22 institution findings?</p> <p>23 MS. O'DELL: Objection to the</p> <p>24 question, vague and unclear.</p>

35 (Pages 134 to 137)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 138</p> <p>1 THE WITNESS: Am I to answer or 2 not answer? 3 MS. O'DELL: If you understand 4 the question. If you don't understand 5 the question, you may ask that it be 6 rephrased. 7 A. Can you rephrase the question? 8 BY MS. BROWN: 9 Q. How did you weight the evidence 10 contained in Hopkins Exhibit 28 in connection 11 with the findings of the FDA? 12 MS. O'DELL: Object to the 13 form. 14 A. I considered the weight of all 15 of the evidence in the whole of the risk of 16 talcum powder in ovarian cancer. This is a 17 small piece of it. 18 BY MS. BROWN: 19 Q. I want to concentrate just on 20 your opinion that there's asbestos in talc. 21 And I want to know, did you weight 22 Dr. Longo's litigation reports the same as 23 the testing by the FDA? 24 MS. O'DELL: Object to the form</p>	<p style="text-align: right;">Page 140</p> <p>1 of the documents that are cited in Hopkins' 2 Exhibit 28? 3 A. No. 4 Q. Do you know who created 5 Hopkins' Exhibit 28? 6 A. Specifically, no. 7 Q. Okay. Do you know whether 8 these represent final or preliminary test 9 results? 10 MS. O'DELL: Object to the 11 form. 12 A. I don't know. 13 BY MS. BROWN: 14 Q. Do you know whether the entries 15 that indicate testing of ore is industrial or 16 cosmetic talc ore? 17 A. I don't. 18 MS. O'DELL: Object to the 19 form. 20 BY MS. BROWN: 21 Q. Other than Hopkins' Exhibit 28, 22 Dr. Longo and the two FDA reports we've 23 discussed, are you relying on anything else 24 to inform your opinion that talcum powder is</p>
<p style="text-align: right;">Page 139</p> <p>1 of the question, misstates her 2 testimony. 3 MS. BROWN: It's a question. 4 There's no testimony. We've got to go 5 off anyway. Let's take a break. 6 THE VIDEOGRAPHER: Going off 7 the record. The time is 11:18 a.m. 8 (Recess taken from 11:18 a.m. 9 to 11:27 a.m.) 10 THE VIDEOGRAPHER: This marks 11 the beginning of disk 2. Back on the 12 record. The time is 11:27 a.m. 13 BY MS. BROWN: 14 Q. Dr. Wolf, before we took a 15 break, we were discussing your opinion that 16 talcum powder contains asbestos. I 17 understand you are relying in part on 18 Dr. Longo's reports for that opinion; is that 19 true? 20 A. Yes. 21 Q. You are also relying on the 22 Exhibit 28 to Dr. Hopkins' deposition. True? 23 A. Yes. 24 Q. And were you provided with any</p>	<p style="text-align: right;">Page 141</p> <p>1 contaminated with asbestos? 2 A. I also have the deposition of 3 Dr. Blount. 4 Q. And what in the deposition of 5 Dr. Blount informs your opinion that talc is 6 contaminated with asbestos? 7 A. Let me get it out. 8 THE WITNESS: It's probably 9 over there. This is not the right 10 reference. There it is. Sorry. I 11 even had it marked. 12 (Witness reviews document.) 13 BY MS. BROWN: 14 Q. Are you relying in part on 15 Dr. Blount's testimony, Dr. Wolf? 16 A. Yes. 17 Q. Have you reviewed Dr. Blount's 18 published articles? 19 A. I have one here from 1991. 20 Q. Did you review that in forming 21 your opinion that talc is contaminated? 22 A. I did review it, but I'm going 23 to have to look at it here one second. 24 (Witness reviews document.)</p>

36 (Pages 138 to 141)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 142</p> <p>1 A. And the question is, did I use 2 this -- this -- this article that I have is 3 from 1991. I'm looking at my references. 4 Yes, I did -- did use this. 5 BY MS. BROWN: 6 Q. And when you say "this," is it 7 your testimony that you are relying on the 8 information contained in Blount's 1991 9 article to inform your opinion that talc is 10 contaminated with asbestos? 11 A. I'm relying on all of the -- 12 all of the references that I have in my list. 13 That's one of them. 14 Q. Well, some of these references 15 have nothing to do with Johnson's baby 16 powder, right? 17 A. Yes. The references that 18 specifically are the testing for Johnson's 19 baby powder that I'm relying on for my 20 statement that some baby -- some talcum 21 powder product contains asbestos, are the 22 Hopkins data that I showed you, the Longo 23 testing and the deposition of Dr. Blount. 24 Q. So did you write the paragraph</p>	<p style="text-align: right;">Page 144</p> <p>1 products that are contaminated with asbestos 2 are Johnson & Johnson baby powder products? 3 A. Let me look at one thing and 4 then I'll answer your question. 5 (Witness reviews document.) 6 A. Given that the market of 7 Johnson -- of talcum powder products is -- 8 the majority is Johnson's baby powder and 9 Johnson & Johnson products. I'm assuming 10 that in this, where they've got consumer 11 products, that some of those were Johnson & 12 Johnson. 13 BY MS. BROWN: 14 Q. And you understand that some of 15 the consumer products they tested did not 16 have asbestos? 17 A. Yes. 18 Q. Did you understand that? 19 A. I understand that. 20 Q. Okay. What informs your 21 opinion that the products that were all 22 tested in 1976, in which he found asbestos, 23 were Johnson & Johnson products? 24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 143</p> <p>1 that cites, for example, Paoletti and Rohl 2 1976? 3 A. Yes. 4 Q. Okay. Why would you include 5 Rohl 1976 as evidence that talcum powder -- 6 Johnson's baby powder is contaminated? 7 A. I'd have to read it again to 8 tell you what specifically I pulled out of 9 there. Would you like me to do that? 10 Q. Let me see if I can ask you 11 some questions and save us some time. The 12 article -- 13 MS. O'DELL: Excuse me. Feel 14 free to turn to it, if you'd like. 15 THE WITNESS: All right. 16 MS. O'DELL: I believe it's in 17 this one. 18 BY MS. BROWN: 19 Q. The article reports on some 20 products tested being contaminated and others 21 not. Do you remember that? 22 A. Yeah. 23 Q. And what information are you 24 relying on to support your opinion that the</p>	<p style="text-align: right;">Page 145</p> <p>1 form. 2 A. That each one specifically that 3 was tested is a Johnson & Johnson product? 4 Is that what you're asking me? 5 BY MS. BROWN: 6 Q. Are you relying on Rohl 1976 to 7 support your opinion that Johnson's baby 8 powder is contaminated with asbestos? 9 A. This was a consumer talcum 10 powder product. The majority of consumer 11 talcum powder product is Johnson & Johnson. 12 I'm assuming that some of this is Johnson & 13 Johnson. Some of it tested positive. That, 14 along with all of the other evidence, leads 15 many to have the opinion that some Johnson & 16 Johnson talcum powder products contain 17 asbestos. 18 Q. You have assumed that some of 19 the positive test results from Rohl 1976 were 20 Johnson & Johnson products; is that right? 21 MS. O'DELL: Object to the 22 form. 23 A. I'm assuming that some of them 24 were.</p>

37 (Pages 142 to 145)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 146</p> <p>1 BY MS. BROWN:</p> <p>2 Q. And other than your assumption,</p> <p>3 are you relying on any other information for</p> <p>4 your -- to support your opinion that Rohl</p> <p>5 1976 tested Johnson baby powder products and</p> <p>6 found asbestos?</p> <p>7 A. The fact that the majority of</p> <p>8 consumer products are made by Johnson &</p> <p>9 Johnson.</p> <p>10 Q. So Dr. Wolf, as I understand</p> <p>11 your methodology, you've made an assumption,</p> <p>12 that because the majority of talcum powder</p> <p>13 products are made by J&J, the positive</p> <p>14 results in the Rohl study must have included</p> <p>15 J&J products?</p> <p>16 A. I used -- I -- what I'm saying</p> <p>17 is that this supports all the other evidence</p> <p>18 that there's been asbestos found in some</p> <p>19 Johnson & Johnson products.</p> <p>20 Q. Right. But my question was a</p> <p>21 little different. You've made an assumption,</p> <p>22 that because J&J sells a lot of talcum powder</p> <p>23 products, they must be one of the positive</p> <p>24 test results in the Rohl 1976 article. True?</p>	<p style="text-align: right;">Page 148</p> <p>1 that -- that the majority of the products are</p> <p>2 Johnson -- sold products -- consumer products</p> <p>3 are Johnson & Johnson, that I -- I do assume</p> <p>4 that some of the ones that were tested in</p> <p>5 this are Johnson & Johnson. I took that</p> <p>6 information and put it with the other</p> <p>7 information to make my conclusion.</p> <p>8 BY MS. BROWN:</p> <p>9 Q. And if you were wrong about</p> <p>10 your assumption regarding Rohl 1976, how</p> <p>11 would that affect your opinion here?</p> <p>12 A. I don't believe it would affect</p> <p>13 my opinion that talcum powder products</p> <p>14 include asbestos. So I don't think it would</p> <p>15 change my opinion.</p> <p>16 Q. So whether Rohl found a</p> <p>17 positive test result for a Johnson & Johnson</p> <p>18 product or not doesn't affect your opinion;</p> <p>19 is that right?</p> <p>20 MS. O'DELL: Objection to the</p> <p>21 form.</p> <p>22 A. My concern is that overall</p> <p>23 multiple testing, over multiple years from</p> <p>24 multiple sites, suggests that some talcum</p>
<p style="text-align: right;">Page 147</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form, it misstates Dr. Wolf's</p> <p>3 testimony.</p> <p>4 A. I don't believe that's what I</p> <p>5 said. I believe that -- my assumption is</p> <p>6 that some of the powder tested in this is</p> <p>7 Johnson & Johnson product. Some of the</p> <p>8 powder tested in this tested positive for</p> <p>9 asbestos.</p> <p>10 In the other studies some of</p> <p>11 the powder tested, some of which was Johnson</p> <p>12 & Johnson, some of which might be from some</p> <p>13 other company, tested positive, and therefore</p> <p>14 the whole of the evidence, in my belief,</p> <p>15 shows that some Johnson & Johnson product --</p> <p>16 talcum powder products contain asbestos.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. You've made an assumption that</p> <p>19 Johnson & Johnson's baby powder products that</p> <p>20 were tested by Rohl in 1976 contained</p> <p>21 asbestos, correct?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. My answer remains the same</p>	<p style="text-align: right;">Page 149</p> <p>1 powder product contains asbestos.</p> <p>2 BY MS. BROWN:</p> <p>3 Q. Have you formed an opinion</p> <p>4 about what percentage of Johnson & Johnson</p> <p>5 talcum powder product contains asbestos?</p> <p>6 A. I don't care what percentage</p> <p>7 does. If there's any in it, it's too much.</p> <p>8 Q. Okay. But we're going to get</p> <p>9 through this so much faster if you just</p> <p>10 listen to my question. Which was, have you</p> <p>11 formed an opinion about how much of Johnson &</p> <p>12 Johnson's talcum powder products are</p> <p>13 contaminated with asbestos?</p> <p>14 MS. O'DELL: Excuse me,</p> <p>15 Dr. Wolf. Move to strike the</p> <p>16 commentary. You may answer the</p> <p>17 questions in any way you feel</p> <p>18 appropriate, Dr. Wolf. So object to</p> <p>19 the form of the question.</p> <p>20 A. Sorry, you're going to -- what</p> <p>21 your question was again.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. I'll re-ask it, rather than</p> <p>24 have you read the realtime, Doctor. Have you</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 150</p> <p>1 attempted to quantify or estimate what 2 percentage of Johnson & Johnson powder -- 3 Johnson & Johnson baby powder products are 4 contaminated with asbestos? 5 MS. O'DELL: Object to the 6 form. 7 A. I haven't attempted to quantify 8 what percentage of Johnson & Johnson baby 9 powder products contain asbestos. I hold the 10 opinion that if any of it contains asbestos, 11 it's too much. 12 BY MS. BROWN: 13 Q. Have you formed an opinion 14 about what type of asbestos is contaminating 15 Johnson & Johnson baby powder products? 16 A. It doesn't matter to me. All 17 types of asbestos are carcinogenic. 18 Q. And that wasn't my question. 19 My question was, have you formed an opinion 20 about what type of asbestos is contaminating 21 Johnson & Johnson's baby powder products? 22 MS. O'DELL: Excuse me. Object 23 to the form of the question, asked and 24 answered.</p>	<p style="text-align: right;">Page 152</p> <p>1 dangerous. 2 BY MS. BROWN: 3 Q. And in terms of your 4 methodology for analyzing the epidemiology in 5 this case, have you done that with an 6 assumption that the talcum powder evaluated 7 in the epi contained asbestos? 8 A. That question is not clear to 9 me. Are you -- 10 Q. Let me rephrase. I understand 11 you looked at a number of epi studies in 12 forming your opinion here, correct? 13 A. Yes. 14 Q. Have you made the assumption 15 that the talcum powder that was studied in 16 those epi studies contained asbestos? 17 MS. O'DELL: Object to the 18 form. 19 A. So I'm going to say that when 20 I -- when reviewing all of the studies, I 21 wasn't really thinking specifically about the 22 components of talcum powder product. I was 23 looking at the epidemiology of the findings 24 of talcum powder product and its risk for</p>
<p style="text-align: right;">Page 151</p> <p>1 A. I'll restate that. Because it 2 doesn't matter to me what -- which type of 3 asbestos might be contained in a sample of 4 Johnson & Johnson's talcum powder product, I 5 don't have any opinion as to what type. 6 BY MS. BROWN: 7 Q. Do you have an opinion as to 8 how much contamination is in each individual 9 bottle of Johnson & Johnson's baby powder? 10 MS. O'DELL: Object to the 11 form. 12 A. Because it doesn't matter to me 13 how much there is, whether it's a small 14 amount, a large amount, a medium amount, my 15 concern is that if there's any in it, it's 16 dangerous; I haven't formed an opinion about 17 how much there is. 18 BY MS. BROWN: 19 Q. Do you believe that there's no 20 amount of asbestos that's safe? 21 MS. O'DELL: Object to the 22 form. 23 A. I believe that any amount of 24 asbestos in talcum powder product is</p>	<p style="text-align: right;">Page 153</p> <p>1 ovarian cancer, and then separately, in 2 investigating and looking at all the 3 components of talcum powder as a way to 4 explain the results of the epidemiology 5 studies. 6 So I'm not -- in the end, as a 7 whole -- it's part of the whole, but 8 specifically looking at the epidemiology 9 studies, that wasn't my biggest concern. My 10 concern was, did the use of genital talcum 11 powder increase the risk of ovarian cancer? 12 BY MS. BROWN: 13 Q. Do you believe that talc that's 14 not contaminated with asbestos can cause 15 ovarian cancer? 16 A. I think of the product as a 17 whole versus separate, and my concern is that 18 in the talcum powder product, whether or not 19 a particular sample has asbestos, yes, there 20 are other things in there that can be 21 carcinogenic and inflammatory and cause 22 ovarian cancer. 23 Q. Do you believe that talcum 24 powder without asbestos causes ovarian</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 154</p> <p>1 cancer?</p> <p>2 MS. O'DELL: Objection to the</p> <p>3 form.</p> <p>4 A. I believe that asbestos is one</p> <p>5 of the products -- one of the components of</p> <p>6 talcum powder that causes carcinogenesis of</p> <p>7 the ovary or cancer of the ovary, but I think</p> <p>8 that in a specific sample, whether or not</p> <p>9 there's asbestos, there's enough other</p> <p>10 products that can be carcinogenic that, yes,</p> <p>11 I think it's still at risk.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. Okay. Have you reviewed, in</p> <p>14 connection with your opinions, Doctor, IARC's</p> <p>15 review of asbestos?</p> <p>16 A. Yes.</p> <p>17 Q. Do you believe that asbestos is</p> <p>18 a recognized cause of ovarian cancer?</p> <p>19 A. Yes.</p> <p>20 Q. Have you ever diagnosed a</p> <p>21 patient with ovarian cancer caused by</p> <p>22 asbestos?</p> <p>23 A. I have, that I can recall, at</p> <p>24 least one patient.</p>	<p style="text-align: right;">Page 156</p> <p>1 physician when you treated this patient?</p> <p>2 A. At MD Anderson.</p> <p>3 Q. You'd agree that the literature</p> <p>4 that IARC relies upon in finding that</p> <p>5 asbestos can cause ovarian cancer is in the</p> <p>6 occupational context?</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form.</p> <p>9 A. Yes, I would say that they</p> <p>10 looked at inhalation generally and dermal</p> <p>11 contact, yes.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. And they looked at that in the</p> <p>14 heavy occupational exposure context, correct?</p> <p>15 MS. O'DELL: Objection to the</p> <p>16 form.</p> <p>17 A. You know, I'd have to look at</p> <p>18 the wording in that IARC again to answer that</p> <p>19 question.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. Dr. Wolf, I'll hand -- we'll</p> <p>22 mark as Exhibit 10, IARC's monograph on</p> <p>23 asbestos and ovarian cancer.</p> <p>24</p>
<p style="text-align: right;">Page 155</p> <p>1 Q. And what was the asbestos</p> <p>2 exposure of this patient encounter?</p> <p>3 A. I don't recall. It was a long</p> <p>4 time ago.</p> <p>5 Q. And you documented in a</p> <p>6 patient's chart that you believed her ovarian</p> <p>7 cancer was caused by asbestos?</p> <p>8 A. I'd have to go back and review</p> <p>9 the chart. I don't think I, personally, put</p> <p>10 that in the chart. I'd have to review the</p> <p>11 chart. It may be in her chart, in the</p> <p>12 pathology report that they saw evidence of</p> <p>13 fibers in the cancer. It might be it was her</p> <p>14 exposure. I just remember one patient where</p> <p>15 I went and reviewed the literature on</p> <p>16 asbestos in ovarian cancer because that was</p> <p>17 the concern.</p> <p>18 Q. Did this patient have</p> <p>19 occupational exposure to asbestos?</p> <p>20 A. I don't recall.</p> <p>21 Q. You --</p> <p>22 A. And I don't have access to her</p> <p>23 medical records.</p> <p>24 Q. Where were you the treating</p>	<p style="text-align: right;">Page 157</p> <p>1 (Deposition Exhibit 10 marked</p> <p>2 for identification.)</p> <p>3 BY MS. BROWN:</p> <p>4 Q. I'll direct your attention to</p> <p>5 page 256. Did you review all of the studies</p> <p>6 in this monograph before forming your</p> <p>7 opinions in this case?</p> <p>8 MS. O'DELL: Do you have a copy</p> <p>9 for me, Counsel?</p> <p>10 A. Are you asking did I separately</p> <p>11 read all of the articles in this monograph?</p> <p>12 BY MS. BROWN:</p> <p>13 Q. Yes.</p> <p>14 A. The references?</p> <p>15 MS. O'DELL: Counsel, excuse</p> <p>16 me. Can I just ask, is this going to</p> <p>17 be Exhibit 10?</p> <p>18 MS. BROWN: No, I marked</p> <p>19 Exhibit 10.</p> <p>20 MS. O'DELL: Okay. This is --</p> <p>21 A. I don't think I reviewed all of</p> <p>22 these articles.</p> <p>23 BY MS. BROWN:</p> <p>24 Q. Do the asbestos studies that</p>

40 (Pages 154 to 157)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 158</p> <p>1 IARC relies on in what we've marked as 2 Exhibit 10, inform your opinion in this case? 3 A. My opinion that asbestos causes 4 cancer? 5 Q. Yes. 6 A. It's part of the opinion, yes. 7 Q. What do you rely on to support 8 your opinion that asbestos causes ovarian 9 cancer? 10 A. I would say that this and all 11 of the literature. And some of this 12 literature, I believe, is in my 13 contributing -- contributing materials that I 14 reviewed. The Reid paper, the Langseth 15 paper, the Magnani paper. Just didn't read 16 them all, but all of their references. 17 Q. And you would agree that the 18 studies that IARC reviewed were in the heavy 19 occupational exposure context, correct? 20 MS. O'DELL: Object to the 21 form. 22 A. Occupationally exposed. 23 BY MS. BROWN: 24 Q. Let's look at page 256, the</p>	<p style="text-align: right;">Page 160</p> <p>1 statistically significant increase of ovarian 2 cancer, correct? 3 MS. O'DELL: Object to the 4 form. 5 A. There's an increase, but not a 6 statistically significant increase. 7 BY MS. BROWN: 8 Q. Well, that's an important 9 distinction, isn't it, Doctor? 10 A. So it would be -- it would be 11 stronger evidence if it was statistically 12 significant. I'm not writing it off as not 13 important, because the overall conclusion is 14 that asbestos increases the risk of ovarian 15 cancer. And I certainly wouldn't suggest 16 that anyone expose themselves to asbestos, 17 whether it's an occupational hazard or not, 18 not just for its risk of ovarian cancer, but 19 for the risk of other cancers, lung cancers, 20 pleural cancers, renal cancers. 21 Q. The only studies on which IARC 22 relies to support its conclusion that 23 asbestos causes ovarian cancer that have a 24 statistically significant finding are in the</p>
<p style="text-align: right;">Page 159</p> <p>1 second column, the first full paragraph. 2 "The Working Group noted that a causal 3 association between exposure to asbestos and 4 cancer of the ovary was clearly established 5 based on five strongly positive cohort 6 mortality studies of women with heavy 7 occupational exposure to asbestos." 8 Right? 9 MS. O'DELL: Object to the 10 form. 11 BY MS. BROWN: 12 Q. That's what IARC concluded, 13 right? 14 MS. O'DELL: Object to the 15 form. 16 A. Well, that's part of the 17 conclusion. The next study shows that women 18 and girls with environmental but not exposure 19 to -- occupational exposure had positive but 20 not a significant increase in ovarian cancer 21 also. 22 BY MS. BROWN: 23 Q. Right. The environmental 24 studies that IARC considered did not show a</p>	<p style="text-align: right;">Page 161</p> <p>1 heavy occupational context, correct? 2 MS. O'DELL: Object to the 3 form. 4 A. In that paragraph, that's what 5 it says. 6 BY MS. BROWN: 7 Q. Do you believe that studies 8 looking at women who are experiencing heavy 9 occupational exposure to asbestos, can be 10 relied on in the cosmetic exposure context? 11 A. Can be relied on -- 12 Q. Do you think that women 13 experiencing heavy occupational exposure to 14 asbestos are exposed to the same amount of 15 asbestos as women using talcum powder 16 perineally? 17 A. I don't know the answer to 18 that. 19 Q. Have you attempted to quantify 20 the difference between heavy occupational 21 asbestos exposure and perineal talc asbestos 22 exposure? 23 MS. O'DELL: Objection to the 24 form.</p>

41 (Pages 158 to 161)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 162</p> <p>1 A. I haven't attempted to 2 quantify. But if we go back to what I'm 3 talking about here is the talcum powder 4 product, which I believe some of which 5 contains asbestos but also contains fibrous 6 talc, heavy metals and fragrances that are 7 irritating. So it's hard -- it's apples and 8 oranges. It's asbestos occupationally that 9 we're saying here. It's a talcum powder 10 product of which one of the concerning 11 components is asbestos and so it's more than 12 just asbestos. 13 BY MS. BROWN: 14 Q. Are you aware of any scientific 15 literature that has attempted to quantify the 16 difference in exposure between heavy 17 occupational asbestos exposure and cosmetic 18 talcum powder use? 19 A. Of asbestos specifically, is 20 that what you're asking me? What are you 21 asking? 22 Q. Are you aware of any scientific 23 literature that attempts to quantify the 24 difference between how much a woman is</p>	<p style="text-align: right;">Page 164</p> <p>1 environmental asbestos. I don't know if 2 those women used talcum powder in their 3 perineum. But again, talcum powder product 4 is more than asbestos. 5 BY MS. BROWN: 6 Q. Are you relying on the 7 nonstatistically significant findings in the 8 environmental studies of women exposed to 9 asbestos to support your view that cosmetic 10 talcum powder exposure causes ovarian cancer? 11 MS. O'DELL: Object to the 12 form. 13 A. I'm relying on the fact that 14 asbestos is carcinogenic, fibrous talc is 15 carcinogenic, platy talc via IARC is a 16 possible carcinogenic, heavy metals, chromium 17 and nickel are carcinogenic, cobalt is 18 possibly carcinogenic and many of the 19 fragrances in talcum powder product are 20 irritating, that that combination of product 21 causes ovarian cancer in some women and puts 22 any woman who uses it on her perineum at 23 risk -- increased risk for ovarian cancer. 24</p>
<p style="text-align: right;">Page 163</p> <p>1 exposed -- how much asbestos a woman is 2 exposed to in the occupational context versus 3 if she uses a cosmetic talcum powder product 4 that you believe is contaminated with 5 asbestos? 6 MS. O'DELL: Object to the 7 form. 8 A. I'm not aware of any literature 9 that specifically would answer that question 10 because how much, how often the talcum powder 11 is used would have -- would differentiate 12 there. 13 BY MS. BROWN: 14 Q. Are you aware of any scientific 15 support that exposure -- nonoccupational 16 exposure to asbestos causes ovarian cancer? 17 MS. O'DELL: Object to the 18 form, asked and answered. 19 A. So these papers referred here, 20 in fact the Reid paper, suggests that in 21 nonoccupational exposure, there's an 22 increase, although not a statistically 23 significant risk of ovarian cancer in women 24 exposed to what would be presumed to be</p>	<p style="text-align: right;">Page 165</p> <p>1 BY MS. BROWN: 2 Q. Other than the nonstatistically 3 significant studies discussed in IARC's 4 monograph on asbestos, are you aware of any 5 scientific support linking asbestos to 6 ovarian cancer outside of the heavy 7 occupational context? 8 MS. O'DELL: Object to the 9 form, asked and answered. 10 A. I'm going to say I'm not aware 11 of that, but it doesn't form my opinion. I'm 12 going to go back to -- and I know I keep 13 repeating the same thing over again -- it's 14 not the asbestos alone. Asbestos is one of 15 the -- one of the issues that's a component 16 of talcum powder product that I'm concerned 17 about, that I believe the combination of all 18 of those things can increase the risk of 19 ovarian cancer. 20 BY MS. BROWN: 21 Q. Isn't it important for you to 22 know or have established how much asbestos 23 you believe is contaminating baby powder 24 products before you can make that opinion?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 166</p> <p>1 MS. O'DELL: Object to the 2 form. 3 A. To me it is not and that's 4 because if -- if things work in an additive 5 or synergistic way, the amount of asbestos 6 that on its own might increase or not 7 increase the risk of ovarian cancer is 8 separate from the amount of asbestos that in 9 combination with all of the other components 10 might increase the risk of ovarian cancer. 11 BY MS. BROWN: 12 Q. What scientific support do you 13 have for your opinion that asbestos works in 14 an additive way with the other constituents 15 of talcum powder to increase a woman's risk 16 for ovarian cancer? 17 A. I don't know that specifically 18 for asbestos, but I know that in general, 19 cancer doesn't occur because of one thing; it 20 occurs because of multiple things. And that 21 toxins can work in combination and that 22 causes of cancer can work in combination. 23 For instance, the human papilloma virus 24 causes cervical cancer, but if you smoke on</p>	<p style="text-align: right;">Page 168</p> <p>1 know, as far as my understanding, there isn't 2 a study that's taken one out and looked at 3 the difference in carcinogenicity, whether 4 one or the other is not there, but it doesn't 5 matter to me because they're there. Asbestos 6 is carcinogenic. Heavy metals are 7 carcinogenic. Nickel and chromium. Platy 8 talc is possibly carcinogenic. Fibrous talc 9 is asbestos. It's carcinogenic. 10 BY MS. BROWN: 11 Q. Is there a threshold exposure 12 to asbestos in your mind that is needed to 13 cause ovarian cancer? 14 A. Are you asking about asbestos 15 on its own? 16 Q. Asbestos on its own. 17 A. I'm not aware what that 18 threshold is. 19 Q. Have you attempted to survey 20 the literature to see if there is any 21 scientific studies examining whether there is 22 a threshold level of asbestos exposure that 23 causes ovarian cancer? 24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 167</p> <p>1 top of that, your risk of cervical cancer is 2 greater than if you don't smoke. 3 So things can be additive and 4 are synergistic. I don't know if these are 5 additive and/or synergistic. My concern is 6 that they're all toxic and more than likely, 7 I suspect, there are some additivity plus or 8 minus synergism. 9 Q. So if I understand you, 10 Dr. Wolf, you have an understanding generally 11 that multiple factors can work together to 12 cause cancer; is that fair? 13 A. That's correct. 14 MS. O'DELL: Object to form. 15 BY MS. BROWN: 16 Q. As it relates to whether or not 17 multiple elements of a talcum powder product 18 work together to form -- to increase a 19 woman's risk of cancer, you're not aware of 20 any scientific support for that opinion. 21 True? 22 MS. O'DELL: Object to the 23 form. 24 A. I'm not aware of -- as far as I</p>	<p style="text-align: right;">Page 169</p> <p>1 form. 2 A. Hold on one second. Because 3 I'm looking on my papers about an asbestos 4 exposure, but those are not human studies. 5 So my -- my brain says how I would test that, 6 would be to give humans varying amounts of 7 asbestos knowing what you're giving them and 8 seeing who got cancer or not, and that study 9 hasn't been done and can't be done. 10 BY MS. BROWN: 11 Q. And other than kind of your gut 12 or your understanding about how cancer works, 13 is there anything else you're relying on in 14 the scientific literature to support this 15 idea that asbestos is working in combination 16 with something else in talcum powder to 17 increase a woman's risk for ovarian cancer? 18 MS. O'DELL: Object to the 19 form. 20 A. So I'm going to step back and 21 say that my point is that all of those 22 components are toxic in talcum powder. How 23 much asbestos is in there on its own doesn't 24 matter to me because if it's in there and</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 170</p> <p>1 this is in there and this is in there and 2 this is in there, and what I mean is fibrous 3 talc, platy talc, heavy metal, irritating 4 fragrances, it doesn't matter to me how much 5 asbestos is in there. If there's a sample of 6 baby powder that doesn't have asbestos in 7 there, it doesn't matter, because all of 8 those other things also are carcinogenic or 9 possibly carcinogenic or irritating and 10 inflammatory. 11 BY MS. BROWN: 12 Q. So in forming your opinions in 13 this case, Dr. Wolf, it is not important to 14 you to know the chemical composition of an 15 individual bottle of talcum powder; is that 16 right? 17 MS. O'DELL: Object to the 18 form. 19 A. In women who use talcum powder 20 on their perineum, if they're using it 21 regularly, whatever -- however that is 22 defined as once a day, once a week, twice a 23 day, over a period of years they're going to 24 be exposed to more than one bottle of baby --</p>	<p style="text-align: right;">Page 172</p> <p>1 you're going to change your testimony from 2 earlier this morning? 3 MS. O'DELL: Object to the 4 commentary. She's not changing her 5 testimony. She's referred to 6 Dr. Crowley numerous times in her 7 deposition thus far. 8 BY MS. BROWN: 9 Q. Dr. Wolf, you remember telling 10 me this morning you didn't look at anybody's 11 expert report before you wrote yours, right? 12 A. Yes. But I was incorrect, and 13 I'm clarifying it now, because I did see 14 Dr. Crowley's report and I did see 15 Dr. Longo's report. 16 Q. Did you rely on Dr. Crowley's 17 report in forming the opinions in your 18 report? 19 A. About the fragrances, yes. 20 Q. When did you see Dr. Crowley's 21 report? 22 A. Sometime before I turned my 23 report in so that I had time to review it. 24 Q. Did you see a draft version of</p>
<p style="text-align: right;">Page 171</p> <p>1 of talcum powder product. And so whether one 2 of those bottles did or did not have asbestos 3 in it doesn't matter to me. 4 BY MS. BROWN: 5 Q. Because in your view, there are 6 other things in talcum powder that cause 7 cancer? 8 A. Because there are other things 9 in talcum powder that are carcinogenic or 10 possibly carcinogenic, and if a woman has 11 used more than one bottle over her lifetime, 12 the chances are pretty high that one of those 13 bottles did contain asbestos in addition to 14 the others. 15 Q. Is it your opinion that the 16 fragrances in Johnson & Johnson's baby powder 17 cause ovarian cancer? 18 A. No, I never stated that. It's 19 my opinion that some of them are known 20 irritants or can be inflammatory, and that 21 was from Dr. Crowley's report, which I did 22 see before I wrote my report, his expert 23 report. 24 Q. Time-out. Time-out. Are we --</p>	<p style="text-align: right;">Page 173</p> <p>1 Dr. Crowley's report? 2 A. I think I saw his final report. 3 Q. How many days did you spend 4 reviewing Dr. Crowley's report? 5 MS. O'DELL: Object to the 6 form. 7 A. I don't recall. 8 BY MS. BROWN: 9 Q. What information did you use or 10 rely on from Dr. Crowley's report? 11 A. I can pull it up, but I believe 12 you have a list of all of the things that 13 were in there and looking at them, what they 14 were -- what was known about all of the 15 different components. 16 Q. Did you do anything to verify 17 the accuracy of Dr. Crowley's list of 18 components of talcum powder? 19 MS. O'DELL: Object to the 20 form. 21 A. Such as? What are you 22 suggesting? 23 BY MS. BROWN: 24 Q. Did you do anything, as an</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 174</p> <p>1 independent expert witness, to check the list 2 that you received from Dr. Crowley? 3 MS. O'DELL: Object to the 4 form. 5 A. I don't know how I could have 6 done that because I didn't have the list of 7 what was in there myself. And I don't -- 8 so -- and I don't do the testing myself. I 9 relied on the expert, that he tested and 10 found those things in the report, in the 11 fragrance -- or in the product, sorry. 12 BY MS. BROWN: 13 Q. And is it your opinion that 14 some of the elements on Dr. Crowley's list 15 increase a woman's risk of ovarian cancer? 16 A. No. It's my opinion that some 17 of the ingredients on the list are 18 inflammatory. And I know that inflammation 19 plays a role in the development and 20 progression of ovarian cancer. 21 Q. Are you relying on any 22 scientific literature to support your 23 opinion, that some of the chemicals in 24 Johnson & Johnson's baby powder cause an</p>	<p style="text-align: right;">Page 176</p> <p>1 Dr. Crowley's list, are you relying on the 2 presence of those in the baby powder product 3 to support your opinion that it increases a 4 woman's risk of ovarian cancer? 5 A. I believe it's one of the 6 things that could. 7 Q. So what I want to know is what 8 ingredients do you believe could increase a 9 woman's risk of ovarian cancer, and then, 10 two, what scientific support you have for 11 that? 12 MS. O'DELL: Excuse me. Object 13 to the form. 14 A. I never said that those 15 ingredients themselves could increase the 16 risk of ovarian cancer. What I'm saying is 17 that some of the ingredients can be 18 inflammatory. Inflammation is associated 19 with development and progression of ovarian 20 cancer. Those fragrances on their own -- 21 excuse me, in conjunction with all of the 22 other components of talcum powder are 23 concerning to me. 24</p>
<p style="text-align: right;">Page 175</p> <p>1 inflammatory reaction that can lead to 2 cancer? 3 MS. O'DELL: Object to the 4 form. 5 A. I'm relying on the literature 6 that says ovarian cancer is related to 7 inflammation, both development and 8 progression, and knowing that those are 9 inflammatory, I have a concern about them. 10 BY MS. BROWN: 11 Q. Do you have any scientific 12 support that the chemicals in Johnson & 13 Johnson's baby powder are inflammatory in 14 human beings? 15 MS. O'DELL: Object to the 16 form. 17 A. I'd have to look at the report 18 of how they were all tested. I know that -- 19 I'm assuming most of it was in animals, not 20 in humans. So I'd have to look at the 21 report. 22 BY MS. BROWN: 23 Q. Are you relying on the presence 24 of certain of the chemicals listed on</p>	<p style="text-align: right;">Page 177</p> <p>1 BY MS. BROWN: 2 Q. And what support do you have in 3 the scientific literature that would lead you 4 to be concerned about the inflammatory 5 process you just described? 6 A. Oh, in ovarian cancer? 7 Q. No, with these chemicals, what 8 support do you have -- the list of 9 fragrances, what support do you have that 10 those elements cause inflammation that could 11 lead to cancer in humans? 12 MS. O'DELL: Object to the 13 form. 14 A. I never said I had that 15 evidence. What I'm saying, is that the 16 expert report says that many of them are 17 inflammatory and that I know that 18 inflammation has -- plays a large role in 19 ovarian cancer and there's more and more 20 papers suggesting that, and that this is one 21 of the components of talcum powder product 22 that I'm concerned about. 23 BY MS. BROWN: 24 Q. And do you have any evidence</p>

45 (Pages 174 to 177)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 178</p> <p>1 that those elements have been tested in human 2 beings, have caused inflammation in human 3 beings? 4 MS. O'DELL: Object to the 5 form. 6 A. I would have to review his 7 report again. My -- so I can't answer that 8 question offhand. I would suspect that most 9 of these were tested in animals, not in human 10 beings. 11 BY MS. BROWN: 12 Q. For purposes of your opinion, 13 Dr. Wolf, are you relying on a finding in 14 animals of inflammation, to support your 15 opinion that talcum powder causes ovarian 16 cancer? 17 MS. O'DELL: Object to the 18 form. 19 A. No. What I'm relying on is -- 20 let me clarify it. What I'm relying on is 21 that these cause inflammation, even if it's 22 in animals. They are part of the talcum 23 powder product and concerning to me, in 24 addition with all of the other parts of</p>	<p style="text-align: right;">Page 180</p> <p>1 of ovarian cancer. 2 BY MS. BROWN: 3 Q. Other than your understanding 4 that some of the fragrances have been 5 inflammatory in animals, is there anything 6 else you're relying on to support your 7 opinion, that the presence of the fragrances 8 in Johnson & Johnson's baby powder increase a 9 woman's risk of ovarian cancer? 10 MS. O'DELL: Object to the 11 form. 12 A. I'm just reading the question 13 again. The fact that I know that 14 inflammation in a proinflammatory state is 15 related to the development of ovarian cancer 16 and the progression of ovarian cancer, I'm 17 concerned about anything in talcum powder 18 product that would increase -- potentially 19 increase inflammation. 20 BY MS. BROWN: 21 Q. How -- have you made a 22 determination of how much of the fragrances 23 are present in the talcum powder product? 24 A. I do not know that.</p>
<p style="text-align: right;">Page 179</p> <p>1 talcum powder that are concerning, asbestos, 2 fibrous talc, platy talc, heavy metals. 3 BY MS. BROWN: 4 Q. What support do you have that 5 the inflammation you're referring to leads to 6 cancer? 7 MS. O'DELL: Object to the 8 form. 9 BY MS. BROWN: 10 Q. What I'm after is, where are 11 the scientific studies that say this 12 inflammation in an animal caused cancer, of 13 the list of fragrances Dr. Crowley opines on? 14 MS. O'DELL: Object to the 15 form, asked and answered. 16 A. Yeah, I believe I've already 17 answered that question. I don't have a study 18 that I can point to that says, using this 19 agent it produced cancer, in this agent that 20 it produced cancer. But if they're 21 inflammatory, that's concerning enough to me, 22 especially with ovarian cancer, that they 23 could play a role in the toxicity of talcum 24 powder on the perineum to increase the risk</p>	<p style="text-align: right;">Page 181</p> <p>1 Q. Isn't it important for you in 2 forming your opinion, to know the amount of 3 exposure that a woman would get from 4 fragrances in talcum powder? 5 MS. O'DELL: Object to form. 6 A. I'm going to go back to what I 7 said about asbestos and the amount. First of 8 all, I don't know how you would quantify the 9 amount when I don't know what a dose is, how 10 often someone uses it, how much they use, how 11 long they used talcum powder product. And 12 then in addition, each individual woman, her 13 makeup, her response is going to be 14 different. 15 And so given that there isn't 16 testing of dosing to see if each of these 17 individual things increases the risk of 18 ovarian cancer and there's some concern that 19 they increase inflammation, my concern is 20 that any amount is worrisome. 21 BY MS. BROWN: 22 Q. And the basis for your opinion 23 that it's worrisome is your understanding 24 that in some dose, these chemicals can cause</p>

Judith K. Wolf, M.D.

Page 182	Page 184
<p>1 inflammation in animal models. True?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. And more than that, that</p> <p>5 inflammation can cause -- be one of the</p> <p>6 causes of ovarian cancer and this is</p> <p>7 something that's in a product that has</p> <p>8 multiple things that have been associated</p> <p>9 with increased inflammation and/or</p> <p>10 carcinogenicity of the ovaries.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. And tell me, Doctor, I</p> <p>13 understand you believe that there is asbestos</p> <p>14 in baby powder, right, we talked about that?</p> <p>15 A. I have seen data to support</p> <p>16 that there is asbestos in some baby powder</p> <p>17 product.</p> <p>18 Q. And you have not made a</p> <p>19 determination as to how much may be in baby</p> <p>20 powder, correct? How much asbestos?</p> <p>21 MS. O'DELL: Objection to the</p> <p>22 form --</p> <p>23 A. My concern is that I don't -- I</p> <p>24 don't know specifically how much, and I don't</p>	<p>1 form.</p> <p>2 A. I believe I've answered this</p> <p>3 question multiple times, that these fragrance</p> <p>4 ingredients, some of them cause inflammation,</p> <p>5 at least in animals, that ovarian cancer, one</p> <p>6 of the causes, is a proinflammatory state and</p> <p>7 inflammation can also enhance the progression</p> <p>8 of ovarian cancer. And so if there's a</p> <p>9 product that I know contains -- one of the</p> <p>10 components can cause inflammation, and I</p> <p>11 don't know what level is safe, I don't know</p> <p>12 that I can answer that there's a safe level.</p> <p>13 BY MS. BROWN:</p> <p>14 Q. Are you familiar with talc</p> <p>15 pleurodesis?</p> <p>16 A. Yes.</p> <p>17 Q. You understand that that is a</p> <p>18 procedure in which talc is placed inside a</p> <p>19 person's lung for its inflammatory response,</p> <p>20 correct?</p> <p>21 A. So it's not placed in the lung.</p> <p>22 It's placed in the pleura.</p> <p>23 Q. Pleura. Right?</p> <p>24 A. Yes.</p>
Page 183	Page 185
<p>1 really have a threshold of how much is safe.</p> <p>2 I'm concerned with any.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. And you've not made a</p> <p>5 determination as to how much fragrance is in</p> <p>6 any individual bottle of baby powder,</p> <p>7 correct?</p> <p>8 A. Well, an individual fragrance,</p> <p>9 no, I don't know.</p> <p>10 Q. Is it your testimony that any</p> <p>11 amount, including trace levels of fragrances,</p> <p>12 can cause inflammation that lead to cancer?</p> <p>13 MS. O'DELL: Objection to the</p> <p>14 form.</p> <p>15 A. I don't know how much of the</p> <p>16 fragrances are required to cause</p> <p>17 inflammation. Given that I don't know how</p> <p>18 much is safe, I'm concerned about any amount.</p> <p>19 BY MS. BROWN:</p> <p>20 Q. But do you have scientific</p> <p>21 support for the fact that any amount of</p> <p>22 fragrance can cause inflammation that leads</p> <p>23 to cancer?</p> <p>24 MS. O'DELL: Object to the</p>	<p>1 Q. And the purpose of placing it</p> <p>2 in the pleura is to initiate an inflammatory</p> <p>3 response, correct?</p> <p>4 A. That's correct.</p> <p>5 Q. And that's, in fact, one of the</p> <p>6 reasons that talc is what's used in</p> <p>7 pleurodesis because it produces in large</p> <p>8 quantities, an inflammatory response, right?</p> <p>9 A. So that is one of the reasons</p> <p>10 that talc has been used. It's not used very</p> <p>11 much anymore because a lot of ovarian cancer</p> <p>12 patients get malignant pleural effusions.</p> <p>13 And so I've had a lot of personal experience</p> <p>14 in -- I'm not doing the pleurodesis myself,</p> <p>15 but referring, and most places for malignant</p> <p>16 pleural effusions these days, they don't use</p> <p>17 any kind of chemical pleurodesis. They put</p> <p>18 in a drain, that the patient can drain as</p> <p>19 needed when they're short of breath.</p> <p>20 Q. You, Doctor, have never</p> <p>21 performed talc pleurodesis; is that right?</p> <p>22 A. I have referred patients to my</p> <p>23 colleagues to do it, but I haven't personally</p> <p>24 done it.</p>

47 (Pages 182 to 185)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 186</p> <p>1 Q. Part of your care as a 2 gynecological oncologist includes from time 3 to time referring patients for talc 4 pleurodesis; is that right? 5 MS. O'DELL: Object to the 6 form. 7 A. Referring patients for 8 management of malignant pleural effusion. 9 And I would say that in the last 15, at 10 least, years, none of my patients have had 11 talc pleurodesis or any kind of chemical 12 pleurodesis. They've all had drains placed. 13 BY MS. BROWN: 14 Q. And you're not a pulmonologist, 15 right, Doctor? 16 A. I'm not a pulmonologist. 17 Q. You are not the primary person 18 that patients go to when they're suffering 19 from diseases of the pleura like 20 mesothelioma, correct? 21 MS. O'DELL: Object to the 22 form. 23 A. No. 24</p>	<p style="text-align: right;">Page 188</p> <p>1 that IARC noted is that in -- certainly, talc 2 pleurodesis causes an inflammatory response, 3 right? 4 A. Yes. 5 Q. And that those patients have 6 been followed for decades, to see if that 7 inflammatory response leads to cancer, right? 8 A. Some of those patients. 9 Q. And by and large -- have you 10 reviewed the epidemiology as it relates to 11 patients who have undergone talc pleurodesis? 12 A. Yes. 13 Q. And you would agree with IARC, 14 that the conclusions are that talc 15 pleurodesis does not cause cancer. True? 16 MS. O'DELL: Object to the 17 form. 18 A. So my interpretation of the 19 literature on that, is that it's a -- most of 20 the time it's a one-time application of talc. 21 Many of those patients have a terminal 22 disease and don't live long enough to know 23 what happens down the road. Some of them 24 have been followed a long time, but the talc</p>
<p style="text-align: right;">Page 187</p> <p>1 BY MS. BROWN: 2 Q. And so whether or not talc 3 pleurodesis is and remains the standard of 4 care at a number of institutions treating 5 patients with mesothelioma is not something 6 that you necessarily know; is that fair? 7 MS. O'DELL: Object to the 8 form. 9 A. I would say it's my 10 understanding that in general, talc 11 pleurodesis is not as common as it used to 12 be. 13 BY MS. BROWN: 14 Q. And you would agree with me, 15 Doctor, that talc pleurodesis is something 16 that IARC considered in reviewing the 17 literature on talc, right? 18 MS. O'DELL: Object to the 19 form. Which monograph are you 20 referring to? 21 BY MS. BROWN: 22 Q. On talc. 23 A. Oh, the 2010? Yes. 24 Q. Right. And one of the things</p>	<p style="text-align: right;">Page 189</p> <p>1 pleurodesis, it happens once, maybe twice, 2 but it's not a repeated application of talc. 3 BY MS. BROWN: 4 Q. Have you attempted to quantify 5 the difference between how much talc is 6 applied to the mesothelial cells of the 7 pleura versus how much talc could enter a 8 woman's body from perineal use? 9 MS. O'DELL: Object to the 10 form. 11 A. I haven't done that. I'm not 12 sure how you could do that, unless you 13 measured how much a woman used over time. 14 BY MS. BROWN: 15 Q. You would agree with me that in 16 the pleurodesis context, talc causes an 17 inflammatory response that does not cause 18 cancer, right? 19 MS. O'DELL: Object to the 20 form. 21 A. I would agree that it causes an 22 acute inflammatory response, that's why it's 23 used. And I would say that many of the -- 24 much of -- it's given once, and much of the</p>

48 (Pages 186 to 189)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 190</p> <p>1 time we don't know -- the patients don't live 2 long enough to know if there's any effect. 3 In the patients that have lived long and have 4 been followed, there hasn't seen an increase 5 risk of cancer, but again, it's a one-time 6 application. 7 BY MS. BROWN: 8 Q. And in terms of how much -- of 9 the one-time application, how much talc gets 10 into a person's body, that's not something 11 you know, right? 12 A. No, because I think that if a 13 woman's using it, I don't know how much she's 14 using over time. And although maybe one time 15 using it in the perineum is less than the 16 amount used for talc pleurodesis, if somebody 17 uses talcum powder product in their peroneum 18 daily, monthly, weekly for years, I don't 19 know how that relates to what's used in a 20 one-time talc pleurodesis. 21 Q. Right. You don't have any 22 information or any basis to compare the 23 amount of talc that's injected into a person 24 who's getting talc pleurodesis with the</p>	<p style="text-align: right;">Page 192</p> <p>1 A. I believe that talc, as well as 2 many inert materials can migrate to the 3 ovaries. 4 Q. What other inert materials can 5 migrate to the ovaries? 6 A. Dead sperm, carbon particles, 7 radioactive material that's been studied. 8 Q. Are you aware -- 9 A. Menstrual blood that flows 10 retrograde. 11 Q. What about particles from the 12 exterior of the vagina? Are you aware of any 13 evidence that those particles can migrate to 14 the ovaries? 15 A. So -- I want to say it's in one 16 of the animal studies. There is definitely 17 inflammation of the genital tract with 18 perineal application of rats from talc. It's 19 not necessarily a migration study. 20 Q. So my question is, do you have 21 any scientific support that particles on the 22 exterior of the vagina can migrate up the 23 genital tract to the ovaries? 24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 191</p> <p>1 amount of talc that may or may not migrate up 2 the genital track to the ovaries. True? 3 MS. O'DELL: Object to the 4 form. 5 A. What I'm saying is that I can't 6 compare the two. It's certainly not bottles 7 of talcum powder that -- multiple bottles 8 that are used in pleurodesis. 9 BY MS. BROWN: 10 Q. Do you know how many grams of 11 talcum powder are used in talc pleurodesis? 12 A. I don't remember offhand. 13 Q. Have you attempted to quantify 14 how much talcum powder could ascend the 15 genital tract through perineal dusting? 16 MS. O'DELL: Object to the 17 form. 18 A. Are you asking me have I 19 personally done that? 20 BY MS. BROWN: 21 Q. Well, in connection with your 22 opinion -- I assume your opinions in this 23 case are based on a belief that talc can 24 migrate to the ovaries. True?</p>	<p style="text-align: right;">Page 193</p> <p>1 form. 2 A. So I don't know how to say 3 this. Because of the position of the 4 perineum, because of the opening of the 5 vagina, because of the opening of the cervix, 6 unless a woman has cervical stenosis, and the 7 opening of the fallopian tubes, unless she 8 has her tubes tied or removed, it's an open 9 tract from the outside up through the vagina 10 and to the ovaries in humans. Some animals 11 not, but in humans. And it's generally 12 accepted in the gynecologic community and by 13 the FDA that migration occurs. 14 BY MS. BROWN: 15 Q. And I understand in connection 16 with your report on page 10, you cite to a 17 number of studies that support your opinion; 18 is that right? 19 A. That's correct. 20 Q. And none of these studies 21 involve studying whether talcum powder 22 applied outside of the vagina can travel up 23 to the ovaries; is that right? 24 A. That's correct, in these</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 194</p> <p>1 studies.</p> <p>2 Q. And in fact, none of these</p> <p>3 studies investigate whether any particle</p> <p>4 applied outside of the vagina can travel up</p> <p>5 to the ovaries. True?</p> <p>6 A. Not -- no, that's correct.</p> <p>7 Q. And, in fact, there is no</p> <p>8 evidence in the scientific community at all,</p> <p>9 that would show a talcum powder particle</p> <p>10 outside of the vagina traveling up to the</p> <p>11 ovaries; that investigation has not been</p> <p>12 done, correct?</p> <p>13 MS. O'DELL: Objection to the</p> <p>14 form.</p> <p>15 A. So the studies that I have</p> <p>16 quoted for -- referenced for migration are</p> <p>17 not talcum powder. There are other inert</p> <p>18 substances. The studies on talcum powder</p> <p>19 were not on the perineum in the vagina, but</p> <p>20 there's -- there's no reason to think or</p> <p>21 believe, and from my perspective and from the</p> <p>22 perspective of the gynecologic community,</p> <p>23 that any inert substance couldn't travel from</p> <p>24 the outside up into the ovaries. In fact,</p>	<p style="text-align: right;">Page 196</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. So there was a concern for</p> <p>4 that. I think we talked about that earlier.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. I'm talking about the epi that</p> <p>7 looked at women who had used, with their</p> <p>8 partners, talc-dusted condoms and you know</p> <p>9 that epi shows no increased risk of ovarian</p> <p>10 cancer, right?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. So just because those</p> <p>14 studies -- okay. I'm going to say okay, yes.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. How did that body of</p> <p>17 epidemiology, how did you take that into</p> <p>18 account in forming your opinion in this case?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. So I mean, I'm going to say</p> <p>22 that it's a piece of the information, but</p> <p>23 when I look at all of the information as a</p> <p>24 whole, as in epidemiology as far as talcum</p>
<p style="text-align: right;">Page 195</p> <p>1 it's been known for decades, that if a woman</p> <p>2 has that system blocked in some way, if her</p> <p>3 tubes are tied or her tubes are removed or</p> <p>4 she's had a hysterectomy, that reduces her</p> <p>5 risk of ovarian cancer. And before there was</p> <p>6 any hint of what might be coming from the</p> <p>7 outside, the hypothesis in the medical</p> <p>8 community, at least in the gynecologic</p> <p>9 community, is that it's an external substance</p> <p>10 that gets to the ovaries.</p> <p>11 And the fact that that could</p> <p>12 happen is based on the fact that all of these</p> <p>13 other things that are known to travel back</p> <p>14 from the outside. And if something's on the</p> <p>15 outside, it can be pushed up into the inside</p> <p>16 through the vagina by intercourse, by going</p> <p>17 to the bathroom, by wiping, by having --</p> <p>18 riding a bike, by exercising, by walking.</p> <p>19 And I think that's -- that's where I'm going</p> <p>20 to stop.</p> <p>21 BY MS. BROWN:</p> <p>22 Q. And you know that none of the</p> <p>23 talc-dusted condom studies show an increased</p> <p>24 risk of ovarian cancer, right?</p>	<p style="text-align: right;">Page 197</p> <p>1 powder product exposure, the weight of the</p> <p>2 evidence suggests that there is an increased</p> <p>3 risk of ovarian cancer with genital talcum</p> <p>4 powder application.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. Did you -- in considering the</p> <p>7 epidemiology that looked at women whose</p> <p>8 partners had used talc-dusted condoms, did</p> <p>9 you weight that epidemiology differently than</p> <p>10 some of the other studies you considered?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. So I'm going to say that the</p> <p>14 studies I gave the most weight to in the epi</p> <p>15 review, were those that were larger, newer</p> <p>16 meta-analysis or a prospective of the cohort</p> <p>17 studies.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. I think one of the ones you</p> <p>20 pointed us to was Cramer 2016, right?</p> <p>21 A. Yes.</p> <p>22 Q. And you know that -- and how</p> <p>23 did you consider Cramer's findings as it</p> <p>24 related to women who had had tubal ligation?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 198</p> <p>1 A. So I believe he didn't see a 2 difference. I have to look at the paper 3 again. Some of them they saw a difference if 4 the tubes were tied and some of them they 5 didn't and I can't remember. 6 MS. O'DELL: If you need to 7 take a look at the paper. 8 BY MS. BROWN: 9 Q. Let's take a look at the paper 10 and refresh you on what Dr. Cramer found, and 11 I'll ask you some questions about that. 12 A. 2016. This one. 13 Q. That's going to be this one. 14 Doctor, I want to direct you to page 339, and 15 we'll mark it as an exhibit. This will be 16 Wolf 11, Dr. Cramer's 2016 article. And I 17 think you stated in your report that this was 18 an article that you found to be of 19 particularly high quality; is that right? 20 A. Yes. 21 (Deposition Exhibit 11 marked 22 for identification.) 23 BY MS. BROWN: 24 Q. And what -- what's your</p>	<p style="text-align: right;">Page 200</p> <p>1 A. If I know it. I don't always 2 know. 3 Q. The date of the publication 4 with a preference for more recent studies? 5 A. Yes. 6 Q. Okay. And anything else that 7 went into your determination that 8 Dr. Cramer's 2016 study was high quality? 9 MS. O'DELL: Other than what 10 she said previously. 11 A. And also all of the different 12 potential cofactors that are evaluated. 13 BY MS. BROWN: 14 Q. By "cofactors that are 15 evaluated," do you mean that the author 16 controlled for confounders? 17 A. Or at least looked at other 18 things that might have an impact. 19 Q. And one of the things you know 20 that Dr. Cramer found on page 339, is that 21 there was a statistically significant 22 increased risk in women who had had their 23 tubes tied who had used talcum powder, right? 24 A. (Nods head.)</p>
<p style="text-align: right;">Page 199</p> <p>1 definition of a "high-quality case-control 2 study"? 3 A. So I looked at the size of the 4 study, the -- I was trying to focus on the 5 newer studies just because this would be more 6 related to talcum powder products in the last 7 20 or 30 years. Dr. Cramer has expertise in 8 this area. This is something that he studied 9 before. And he also looked at multiple -- 10 multiple -- how often the talc was used and 11 multiple factors that might influence whether 12 there was an impact. 13 Q. So as I understand you, 14 Dr. Wolf, the factors you considered in 15 deeming that a study was, quote/unquote, high 16 quality, include looking at the number of 17 people studied; is that right? 18 A. Uh-huh. 19 Q. The author of the study, 20 correct? 21 A. Uh-huh. 22 Q. The -- 23 A. The expertise of the author. 24 Q. The expertise of the author.</p>	<p style="text-align: right;">Page 201</p> <p>1 Q. Do you see that? 2 A. Yes, I see that. 3 Q. Okay. And that's the opposite 4 of what you would expect, based on your 5 opinion and theory. True? 6 MS. O'DELL: Object to the 7 form. 8 A. If we knew when they had their 9 tubes tied. Did they have their tubes tied 10 before they started using talcum powder, or 11 after, or when? 12 BY MS. BROWN: 13 Q. Well, in any event, what you 14 would expect, Doctor, is that the finding in 15 a woman who had her tubes tied should show 16 less of a relative risk than in those who did 17 not have their tubes tied, based on your 18 theory of migration. True? 19 MS. O'DELL: Object to the 20 form. 21 A. Only if those tubes were tied 22 before she was ever exposed to talcum powder 23 product. 24</p>

51 (Pages 198 to 201)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 202</p> <p>1 BY MS. BROWN:</p> <p>2 Q. And you know Dr. Cramer did an</p> <p>3 analysis of that as well, right?</p> <p>4 A. I don't know that he was able</p> <p>5 to.</p> <p>6 Q. What he said, as you recall, is</p> <p>7 that the number of women who only used talcum</p> <p>8 powder after their tubes were tied were too</p> <p>9 small to even analyze, right?</p> <p>10 A. That's the answer --</p> <p>11 (Simultaneous discussion</p> <p>12 interrupted by reporter.)</p> <p>13 MS. O'DELL: Give me a chance.</p> <p>14 If you need to look at the paper,</p> <p>15 don't -- don't assume based on what</p> <p>16 the question is.</p> <p>17 (Witness reviews document.)</p> <p>18 BY MS. BROWN:</p> <p>19 Q. Doctor, you would agree that,</p> <p>20 based on your theory of migration, you would</p> <p>21 expect to see a significantly decreased risk</p> <p>22 in women who had a tubal ligation. True?</p> <p>23 MS. O'DELL: Doctor, feel free</p> <p>24 to continue to refresh yourself before</p>	<p style="text-align: right;">Page 204</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I'm not sure. I would -- if</p> <p>4 the only way that they might get cancer from</p> <p>5 an ovary is from migration, yes. Unless</p> <p>6 their tubes weren't adequately tied.</p> <p>7 However, if the talc got to their ovaries</p> <p>8 from another source through inhalation, then</p> <p>9 there may still be some confounding and some</p> <p>10 increased risk.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. Is it your opinion, Doctor,</p> <p>13 that talc can get to a woman's ovaries</p> <p>14 through inhalation?</p> <p>15 A. Yes.</p> <p>16 Q. Have you considered the</p> <p>17 findings of the epidemiology as it relates to</p> <p>18 body-only powder use?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. Yes.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. And what have those studies, by</p> <p>24 and large, shown?</p>
<p style="text-align: right;">Page 203</p> <p>1 you answer any questions.</p> <p>2 A. I just want to read the -- I</p> <p>3 want to look at one more thing and then I'll</p> <p>4 answer your question.</p> <p>5 (Witness reviews document.)</p> <p>6 A. I can't find it in the written</p> <p>7 part of the article.</p> <p>8 BY MS. BROWN:</p> <p>9 Q. Doctor, I'm going to withdraw</p> <p>10 the question because I really do want to move</p> <p>11 on. I understand you want to spend some time</p> <p>12 with the study and we can do that on a break.</p> <p>13 MS. O'DELL: She's about to</p> <p>14 answer your question.</p> <p>15 A. I mean, it basically says that</p> <p>16 he didn't have enough women to be able to</p> <p>17 explain why that was the case.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. Okay. So as a concept, though,</p> <p>20 Doctor, you would expect, based on your</p> <p>21 theory, that the epidemiology would show a</p> <p>22 decreased risk of ovarian cancer with powder</p> <p>23 use in women who have their tubes tied before</p> <p>24 they use the powder use, correct?</p>	<p style="text-align: right;">Page 205</p> <p>1 A. That it's -- that there's no</p> <p>2 carcinogenicity.</p> <p>3 Q. The epidemiology shows, by and</p> <p>4 large, no increased risk of ovarian cancer</p> <p>5 with body-only use of talcum powder, correct?</p> <p>6 A. Yes.</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. How did you consider that</p> <p>11 epidemiology in forming your opinion that a</p> <p>12 woman might be exposed to talcum powder</p> <p>13 through inhalation?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. I'm not sure how those two</p> <p>17 things relate.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. If a woman uses talcum powder</p> <p>20 on her body, how is she exposed to the talcum</p> <p>21 powder?</p> <p>22 A. On her skin. I don't know what</p> <p>23 you're asking me.</p> <p>24 Q. Do you think there's</p>

Judith K. Wolf, M.D.

Page 206	Page 208
<p>1 potential -- more of a potential for a woman</p> <p>2 to be exposed from inhaling talcum powder</p> <p>3 when she puts it in her underwear than if</p> <p>4 she's using it on her chest?</p> <p>5 A. I don't know.</p> <p>6 Q. Have you evaluated how much</p> <p>7 talcum powder a woman using body-use-only</p> <p>8 would be exposed to?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. I know that body-use-only does</p> <p>12 not increase carcinogenicity --</p> <p>13 carcinogenesis, I'm sorry. But I'm not</p> <p>14 ruling out that someone who routinely daily</p> <p>15 uses it on the perineum couldn't also have</p> <p>16 inhalation exposure.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. And what support do you have in</p> <p>19 the scientific literature for that opinion?</p> <p>20 A. I would say the finding of talc</p> <p>21 in lymph nodes is one potential -- pelvic</p> <p>22 lymph nodes near the ovary, although the</p> <p>23 pelvic lymph nodes could also come from the</p> <p>24 ovary in the other direction. I mean,</p>	<p>1 case report, do you have any other support in</p> <p>2 the scientific literature that a woman using</p> <p>3 talcum powder perineally would be exposed via</p> <p>4 inhalation?</p> <p>5 A. Hang on one second.</p> <p>6 (Witness reviews document.)</p> <p>7 A. I'm looking at my report and my</p> <p>8 references, but they don't specifically talk</p> <p>9 about perineal application and inhalation.</p> <p>10 All I'm saying, to answer your first</p> <p>11 question, to go back a few, is that -- your</p> <p>12 question was, if somebody had their tubes</p> <p>13 tied before they ever used talcum powder,</p> <p>14 would that negate any increased risk of</p> <p>15 ovarian cancer? And my answer was, if the</p> <p>16 tubes were tied, it couldn't migrate up, but</p> <p>17 there's still the possibility that she could</p> <p>18 have it from inhalation. That's all I'm</p> <p>19 saying.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. And I want to know what support</p> <p>22 you rely on in forming the opinion that a</p> <p>23 woman could inhale talcum powder that could</p> <p>24 reach her ovaries and cause ovarian cancer?</p>
Page 207	Page 209
<p>1 migration could lead to talc in pelvic lymph</p> <p>2 nodes.</p> <p>3 Q. What you're referring to is a</p> <p>4 case report from 2007 that -- by Dr. Cramer?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. Did you know that</p> <p>7 Dr. Cramer was an expert witness for the</p> <p>8 plaintiffs?</p> <p>9 A. I did.</p> <p>10 Q. Did you consider Dr. Cramer's</p> <p>11 work as an expert witness in evaluating and</p> <p>12 reaching the determination that his 2016</p> <p>13 paper was high quality?</p> <p>14 A. No.</p> <p>15 Q. The fact that Dr. Kramer is</p> <p>16 being paid by plaintiffs' lawyers in talcum</p> <p>17 powder litigation did not affect your</p> <p>18 evaluation of his 2016 article; is that</p> <p>19 right?</p> <p>20 A. No.</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 BY MS. BROWN:</p> <p>24 Q. Other than Dr. Cramer's 2007</p>	<p>1 A. I'm going to talk -- say that</p> <p>2 talcum powder has been found not only in the</p> <p>3 lymph nodes but in the ovaries of women, both</p> <p>4 who report using and not using perineal</p> <p>5 talcum powder.</p> <p>6 Q. So you're talking about the</p> <p>7 Heller study, right?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. How does the fact that</p> <p>10 talcum powder has been potentially found in</p> <p>11 the ovaries of women who did not report using</p> <p>12 talcum powder, support your view that a woman</p> <p>13 could inhale talcum powder from perineal use</p> <p>14 and have that powder reach her ovaries and</p> <p>15 cause cancer?</p> <p>16 A. To me it just supports the idea</p> <p>17 that talcum powder can get to the ovaries</p> <p>18 through inhalation.</p> <p>19 Q. And did you read the findings</p> <p>20 of that study as it related to whether or not</p> <p>21 the talcum powder that was allegedly found in</p> <p>22 the ovary induced an inflammatory response?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>

Judith K. Wolf, M.D.

Page 210	Page 212
<p>1 A. So sometimes there was an 2 inflammatory response and sometimes not, is 3 my recollection. 4 BY MS. BROWN: 5 Q. Okay. Let's take a look at the 6 paper. 7 A. Okay. 8 MS. O'DELL: We've been going 9 about an hour and a half. It's 12:45. 10 MS. BROWN: If we could finish 11 Heller, then we can take a break. 12 MS. O'DELL: What do you 13 anticipate on Heller? 14 MS. BROWN: Ten minutes. 15 MS. O'DELL: Okay. Is ten 16 minutes okay with you, Doctor? 17 THE WITNESS: Uh-huh. 18 BY MS. BROWN: 19 Q. Thanks, Doctor. 20 A. So it doesn't look like they 21 looked at inflammation. 22 Q. Hold on one second. And one of 23 the things you know that this -- 24 MS. O'DELL: Are you going to</p>	<p>1 response or not. But what I'm going to tell 2 you, I'm reading their entire results. 3 BY MS. BROWN: 4 Q. I promise you I will point it 5 out to you. I don't want to waste time. 6 This is going to be the first thing we do 7 when we come back. 8 Is it your testimony, based on 9 talc causing an inflammatory response, that 10 leads to cancer? 11 A. Yes. 12 Q. And so how -- when talc -- a 13 talc particle is found, would you expect it 14 to show an inflammatory response? 15 A. What I'm trying to say is, that 16 I don't know the timing of the talc being 17 placed and looking at the specimen, was the 18 entire specimen looked at. When you look at 19 pathology slides, you look at a little piece 20 of the tissue. You don't generally look at 21 the entire tissue. And so it could be that 22 the area that was looked at did not show 23 inflammation and in an area that wasn't in 24 the slide did show inflammation.</p>
Page 211	Page 213
<p>1 mark an exhibit? 2 MS. BROWN: Uh-huh. 3 BY MS. BROWN: 4 Q. I'm trying to find it. We'll 5 take a break and I can find it for you, 6 Doctor. But you know that they reported that 7 the talc that was found did not show evidence 8 of a foreign body reaction. Do you remember 9 that? 10 MS. O'DELL: Object to the 11 form. 12 A. That's not anywhere in the 13 results. 14 BY MS. BROWN: 15 Q. I'll show it to you. We'll 16 take a break and I'll show it to you. Would 17 that be important for you to consider? 18 MS. O'DELL: Object to the 19 form. 20 A. I'm going to say not 21 necessarily, because it depends on did they 22 look at the entire ovary, depends on the 23 timing of when they looked at it, whether 24 there's a response -- an inflammatory</p>	<p>1 Q. In your opinion, can talc be in 2 the ovaries and not cause inflammation? 3 A. No, that's not what I'm saying. 4 I'm saying you might not see it if you don't 5 look at the entire specimen, the entire 6 ovary. 7 MS. BROWN: Let's take a break 8 and have lunch and we'll come back and 9 finish Heller, which I will mark. 10 MS. O'DELL: Okay. 11 THE VIDEOGRAPHER: Going off 12 the record. The time is 12:44 p.m. 13 (Recess taken from 12:44 p.m. 14 to 1:41 p.m.) 15 THE VIDEOGRAPHER: Back on the 16 record. The time is 1:41 p.m. 17 (Deposition Exhibit 12 marked 18 for identification.) 19 BY MS. BROWN: 20 Q. Dr. Wolf, I'm handing you what 21 I've marked as Exhibit 12 to your deposition, 22 and which is the article by Heller from 1996 23 that we were discussing before lunch. 24 A. Yes.</p>

Judith K. Wolf, M.D.

Page 214	Page 216
<p>1 Q. And this is --</p> <p>2 MS. O'DELL: Excuse me, do you</p> <p>3 have a copy for me?</p> <p>4 MS. BROWN: Sorry.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. This is one of the articles</p> <p>7 that you pointed me to in support of your</p> <p>8 opinion that talc particles can migrate to</p> <p>9 the ovaries, correct?</p> <p>10 A. Yes.</p> <p>11 Q. Okay. And you would agree with</p> <p>12 me, though, that this study looked at whether</p> <p>13 or not the talc particles that they allegedly</p> <p>14 found were causing an inflammatory response,</p> <p>15 right?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. Well, in -- in reading that</p> <p>19 full paragraph, they looked at one of the</p> <p>20 specimens for an inflammatory response, out</p> <p>21 of 24.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. And the conclusion was that</p> <p>24 there was no evidence of a response to talc,</p>	<p>1 keep moving.</p> <p>2 (Witness reviews document.)</p> <p>3 A. Okay. Sorry, this one does not</p> <p>4 talk -- they don't mention any -- whether</p> <p>5 they even looked for inflammation.</p> <p>6 MS. O'DELL: Dr. Wolf, for the</p> <p>7 record, you were referring to</p> <p>8 Henderson '71?</p> <p>9 THE WITNESS: Yes.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. So to be clear for the record,</p> <p>12 then, Dr. Wolf, in Heller '96 the case that</p> <p>13 they reported on found no evidence of a</p> <p>14 response to talc, correct?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. They looked at one out of 24</p> <p>18 cases and in that one case, they did not see</p> <p>19 a response to talc.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. And you have no evidence that</p> <p>22 there was anything different in the other 23</p> <p>23 cases. True?</p> <p>24 MS. O'DELL: Object to the</p>
Page 215	Page 217
<p>1 such as foreign body giant cell reactions or</p> <p>2 fibrosis in the tissue, right?</p> <p>3 A. In one out of 24.</p> <p>4 Q. That wasn't my question. That</p> <p>5 was their finding, right?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. Their finding in one out of 24.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. Do you have evidence that in</p> <p>11 the other 23 they saw evidence of an</p> <p>12 inflammatory reaction to talc?</p> <p>13 A. I don't have any evidence that</p> <p>14 they looked at the other 23.</p> <p>15 Q. Do you have any evidence at all</p> <p>16 that talc found in the ovary produces an</p> <p>17 inflammatory response?</p> <p>18 A. Yes.</p> <p>19 Q. And what's that?</p> <p>20 A. So I'm going to look at --</p> <p>21 THE WITNESS: Can I get</p> <p>22 Henderson? Two thousand -- 1971.</p> <p>23 BY MS. BROWN:</p> <p>24 Q. I have it here. Let's just</p>	<p>1 form.</p> <p>2 A. I don't have any evidence on</p> <p>3 the other 23 cases.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. And in the Henderson article</p> <p>6 that you just pointed us to, there's</p> <p>7 similarly no evidence about whether or not</p> <p>8 there was an inflammatory reaction. True?</p> <p>9 A. It doesn't look like they</p> <p>10 looked.</p> <p>11 Q. And the way we got started</p> <p>12 talking about -- and you would agree, based</p> <p>13 on the pleurodesis studies, that it is</p> <p>14 possible for talc to cause an inflammatory</p> <p>15 reaction that does not lead to cancer. True?</p> <p>16 A. In the talc -- in pleurodesis</p> <p>17 studies, that's an acute reaction. The</p> <p>18 inflammation that is concerning to lead to</p> <p>19 cancer is a chronic reaction, not an acute</p> <p>20 reaction.</p> <p>21 Q. And how -- what do you rely on</p> <p>22 for how much exposure to talc takes someone</p> <p>23 from a chronic in- -- an acute inflammatory</p> <p>24 response to a chronic inflammatory response?</p>

55 (Pages 214 to 217)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 218</p> <p>1 MS. O'DELL: Object to the 2 form. 3 A. What do I rely on for how much 4 exposure of talc? Exposure to talc over 5 time, can lead to a chronic response, chronic 6 inflammatory response. If you're looking 7 under the microscope at an ovary or something 8 that has talc in it, in that slide you may or 9 may not see an inflammatory response, either 10 acute or chronic, for several reasons. One, 11 that if the talc has been there a long time, 12 you might be -- not be looking when you see 13 obvious inflammatory response either acute or 14 chronic. The second is that you might not be 15 looking at every part of the specimen, to 16 determine if it's just the section that 17 you're looking at. 18 BY MS. BROWN: 19 Q. Have you attempted to quantify 20 how much exposure over time leads to the 21 chronic inflammation you were just 22 describing? 23 MS. O'DELL: Object to the 24 form.</p>	<p style="text-align: right;">Page 220</p> <p>1 A. I know he was doing some 2 research and I wanted to hear from him about 3 what exactly he was looking at, how he was 4 studying it and what his plans were to try to 5 investigate in an in vitro way, the mechanism 6 by which talc can cause ovarian cancer. 7 Q. Would you agree that the 8 mechanism or the proposed mechanism by which 9 talc can cause ovarian cancer, is not well 10 understood today? 11 MS. O'DELL: Object to the 12 form. 13 A. I would agree that there are 14 several lines of evidence, including all of 15 the body of Dr. Saed's work, as well as 16 Dr. Shukla's paper and Dr. Buz'Zard's paper, 17 that suggest that inflammation plays a role 18 in the carcinogenesis of talcum powder 19 product to cause ovarian cancer. And that 20 the most recent work from Dr. Saed's lab, 21 which he's not the first author but the 22 senior author, shows that there's a dose 23 response for the amount of talc and that it's 24 not just inflammation that secondarily causes</p>
<p style="text-align: right;">Page 219</p> <p>1 A. When I look at the literature 2 as a whole, again, going back to the 3 epidemiology literature that attempted to 4 look at dose response, it seems like the -- 5 that several of the studies suggests that 6 more doses, and I'm putting that in quotes 7 because it's not measured, it's not a 8 specific amount, but more exposure increases 9 the risk of ovarian cancer. And so my 10 inference from that, from putting the whole 11 of the literature together, is that the 12 longer -- the more the dose, the more likely 13 the more inflammation and more cell damage, 14 inflammation causing an oxidative response 15 that then can lead down to DNA damage and, in 16 fact, in Saed's most recent abstract genetic 17 changes from talc. 18 BY MS. BROWN: 19 Q. You billed time to the 20 plaintiff's lawyers for speaking to Dr. Saed; 21 is that right? 22 A. Yes. 23 Q. What was the purpose of that 24 conversation?</p>	<p style="text-align: right;">Page 221</p> <p>1 genetic changes, but there's actual genetic 2 changes in the cells that can be 3 carcinogenic. 4 BY MS. BROWN: 5 Q. You testified earlier, I 6 believe, that the opinion that talc particles 7 can migrate to the ovaries is well accepted 8 in the medical community. Do you remember 9 that? 10 A. That migration of inert 11 substances is well accepted in the medical 12 community and, in fact, by the FDA. 13 Q. And would you consider that to 14 include talcum powder? 15 A. I would. 16 Q. And, in fact, you state in your 17 report on page 17, that, "The evidence 18 supporting migration is robust and 19 universally accepted by the gynecologic 20 community." 21 Right? 22 A. Yes. 23 Q. Now, IARC doesn't agree with 24 that, right?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 222</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. So my sentence here says</p> <p>4 "within the gynecologic community."</p> <p>5 BY MS. BROWN:</p> <p>6 Q. Did you mean to exclude the</p> <p>7 international research on cancer?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. No. I'm saying that my</p> <p>11 sentence here says it's universally accepted</p> <p>12 within the gynecologic community.</p> <p>13 BY MS. BROWN:</p> <p>14 Q. Were you aware that it's</p> <p>15 rejected by IARC?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. My understanding is that it's</p> <p>19 not rejected, that in that report that you're</p> <p>20 referring to, which I think is the 2010</p> <p>21 report, that they -- that the evidence that</p> <p>22 they looked at, they said that it was weak,</p> <p>23 not rejected.</p> <p>24</p>	<p style="text-align: right;">Page 224</p> <p>1 BY MS. BROWN:</p> <p>2 Q. And you would agree with me,</p> <p>3 Doctor, that all of the information you cite</p> <p>4 on pages 10 and 11 was available to the</p> <p>5 International Agency for Research on Cancer</p> <p>6 in 2010. True?</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form.</p> <p>9 A. I'd have to look at everything</p> <p>10 that they reviewed to see if they reviewed</p> <p>11 all of that.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. I'm handing you what we've</p> <p>14 marked as Exhibit 15.</p> <p>15 (Deposition Exhibit 13 marked</p> <p>16 for identification.)</p> <p>17 BY MS. BROWN:</p> <p>18 Q. And I want to start by</p> <p>19 directing your attention to page --</p> <p>20 MS. BROWN: I'm sorry, we have</p> <p>21 a copy for you, Counsel.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. This is IARC monograph on talc,</p> <p>24 2010, and I want to start by directing your</p>
<p style="text-align: right;">Page 223</p> <p>1 BY MS. BROWN:</p> <p>2 Q. And have you looked at any</p> <p>3 additional evidence, other than that which</p> <p>4 IARC considered, which leads you to believe</p> <p>5 that it's universally accepted?</p> <p>6 A. I'd have to look at everything</p> <p>7 that IARC looked at and compare it to what I</p> <p>8 looked at to say if it's different.</p> <p>9 Q. Well, what was your methodology</p> <p>10 in terms of considering the International</p> <p>11 Agency for Research on Cancer's conclusion</p> <p>12 that the evidence for migration is weak?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. You know, I -- as I've stated</p> <p>16 before, I used all of the information as a</p> <p>17 whole, to determine my opinion and my -- and</p> <p>18 when I look at the bulk of the evidence and</p> <p>19 with my experience and with what I know about</p> <p>20 gynecology, there's multiple lines of</p> <p>21 evidence that show that migration of inert</p> <p>22 particles occurs, and that retrograde</p> <p>23 migration occurs.</p> <p>24</p>	<p style="text-align: right;">Page 225</p> <p>1 attention to page 33, under the section</p> <p>2 entitled "Mechanistic and other relevant</p> <p>3 data."</p> <p>4 MS. O'DELL: What page?</p> <p>5 THE WITNESS: Thirty-three.</p> <p>6 MS. BROWN: Sorry, is that 13?</p> <p>7 I may have mismarked it.</p> <p>8 MS. O'DELL: That says that's</p> <p>9 15.</p> <p>10 A. 15.</p> <p>11 MS. BROWN: Should be 13.</p> <p>12 We'll correct it.</p> <p>13 A. Do you want it back?</p> <p>14 BY MS. BROWN:</p> <p>15 Q. Yeah, sorry. Thank you,</p> <p>16 Doctor. Handing back to you what is</p> <p>17 Exhibit 13.</p> <p>18 MS. BROWN: Thank you, Alexis.</p> <p>19 BY MS. BROWN:</p> <p>20 Q. And I want to direct your</p> <p>21 attention to page 33. And this IARC</p> <p>22 monograph on talc, nonasbestiform talc, of</p> <p>23 course, you reviewed in connection with your</p> <p>24 opinions in this case. True?</p>

57 (Pages 222 to 225)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 226</p> <p>1 A. Yes.</p> <p>2 Q. Okay. And you are aware that</p> <p>3 IARC considers the strength of the evidence</p> <p>4 as it relates to a proposed mechanism for</p> <p>5 cancer, correct?</p> <p>6 A. Yes.</p> <p>7 Q. Okay. And you see here on</p> <p>8 page 33 that IARC evaluates those, using</p> <p>9 terms such as "weak," "moderate" or "strong,"</p> <p>10 correct?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. And IARC, if you would</p> <p>13 turn to page 411, evaluated the data as it</p> <p>14 relates to migration, right?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. And I'll direct you, excuse me,</p> <p>19 Doctor --</p> <p>20 A. Are you directing me to</p> <p>21 something specific on this page?</p> <p>22 Q. I am.</p> <p>23 A. Okay.</p> <p>24 Q. I'll direct you to the -- one,</p>	<p style="text-align: right;">Page 228</p> <p>1 you employed to arrive at a conclusion that</p> <p>2 is diametrically opposed to the one IARC</p> <p>3 wrote about in 2010?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. I don't -- I don't believe it's</p> <p>7 diametrically opposed and I believe that when</p> <p>8 I reviewed all of the evidence and from my</p> <p>9 own knowledge of gynecology and practicing</p> <p>10 and my expertise in the last 30 years and</p> <p>11 seeing multiple patients with endometriosis</p> <p>12 and evidence of retrograde menstruation, that</p> <p>13 my opinion is that migration occurs. And</p> <p>14 that I believe that it's the opinion of the</p> <p>15 general gynecology community that migration</p> <p>16 does occur. And another reputable</p> <p>17 institution is the FDA, who says that the</p> <p>18 ability for particulates to migrate is</p> <p>19 indisputable.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. And what you're referring to is</p> <p>22 the 2014 citizen's petition, right?</p> <p>23 A. Yes.</p> <p>24 Q. And do you find that to be a</p>
<p style="text-align: right;">Page 227</p> <p>1 two, three -- fourth paragraph that begins</p> <p>2 with "Perineal exposure."</p> <p>3 A. Okay.</p> <p>4 Q. And you see that IARC reports</p> <p>5 on its review of the studies on potential</p> <p>6 migration. True?</p> <p>7 A. Yes.</p> <p>8 Q. And on balance, what the IARC</p> <p>9 working group concluded was that the evidence</p> <p>10 for retrograde transport of talc to the</p> <p>11 ovaries in normal women is weak, right?</p> <p>12 A. Yes.</p> <p>13 Q. And that is their lowest</p> <p>14 classification of mechanistic evidence,</p> <p>15 correct?</p> <p>16 A. Yes.</p> <p>17 Q. And you believe IARC is a</p> <p>18 reputable international health agency, right?</p> <p>19 A. Yes.</p> <p>20 Q. And so you considered its</p> <p>21 conclusion, that the evidence for retrograde</p> <p>22 migration is weak, right?</p> <p>23 A. I did.</p> <p>24 Q. And so tell me what methodology</p>	<p style="text-align: right;">Page 229</p> <p>1 reliable authority on the review of the</p> <p>2 literature regarding talc and ovarian cancer?</p> <p>3 A. This is not regarding --</p> <p>4 necessarily regarding talc and ovarian</p> <p>5 cancer. It's the idea that things can</p> <p>6 migrate from the perineum through the genital</p> <p>7 tract. That's what I based my opinion on</p> <p>8 that.</p> <p>9 Q. We're talking about two</p> <p>10 different things. You just referenced the</p> <p>11 2014 response to a citizen's petition, right?</p> <p>12 A. Yes.</p> <p>13 Q. And do you -- and in that</p> <p>14 response, the FDA went through its review of</p> <p>15 the literature on talc and ovarian cancer,</p> <p>16 correct?</p> <p>17 A. Yes.</p> <p>18 Q. And do you regard that as</p> <p>19 authoritative and reputable?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. Yes.</p> <p>23 BY MS. BROWN:</p> <p>24 Q. Okay. And one of the things</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 230</p> <p>1 you're pointing to, is the FDA's statement 2 that particles can migrate from the perineum 3 in the vagina to the peritoneal cavity, 4 correct? 5 A. That's correct. 6 Q. And the FDA, of course, doesn't 7 cite to any evidence that talc can migrate 8 from the exterior of the vagina to the 9 ovaries, correct? 10 MS. O'DELL: Object to the 11 form. If you're pointing -- going to 12 point Dr. Wolf to a particular part of 13 the letter, then I would ask you to 14 show it to her. 15 MS. BROWN: Absolutely. 16 MS. O'DELL: So if you need to 17 see the letter -- 18 A. Yeah, let me see the letter. 19 MS. O'DELL: -- to respond to 20 the question, please ask for it. 21 BY MS. BROWN: 22 Q. I'm going to show you the 23 letter and I want to talk about it, but you 24 raised the statement about the particles,</p>	<p style="text-align: right;">Page 232</p> <p>1 response to the citizen's petition by the FDA 2 in 2014? 3 A. I'm sure I did. 4 Q. And, in fact, as support for 5 your opinion that talc applied on the 6 exterior of the vagina can migrate to the 7 ovaries, you referenced a sentence from that 8 letter, right? 9 A. That's correct. 10 Q. Okay. But we agree that the 11 FDA was talking about particles generally, 12 correct? 13 MS. O'DELL: Object to the 14 form. 15 A. The FDA was talking about 16 particulates in general. 17 BY MS. BROWN: 18 Q. Okay. And did you review, and 19 I'll hand you what we've marked as 20 Exhibit 14, the entirety of what the FDA had 21 to say about the epidemiology and the 22 evidence as it relates to talc and ovarian 23 cancer? 24</p>
<p style="text-align: right;">Page 231</p> <p>1 right? 2 MS. O'DELL: She did. But she 3 doesn't have to answer questions about 4 the letter aside from what she said. 5 MS. BROWN: I'm not talking -- 6 MS. O'DELL: If you want to ask 7 specific questions about the letter -- 8 MS. BROWN: I'm going to show 9 her the letter. 10 MS. O'DELL: Then show her the 11 letter. 12 MS. BROWN: Okay. But I can 13 ask lead-up questions about the 14 letter. 15 MS. O'DELL: Right. 16 MS. BROWN: It doesn't have 17 to -- 18 MS. O'DELL: Let me finish. In 19 order to answer any of the questions, 20 counsel asked if you need the letter, 21 please ask for it and I'm sure she'll 22 provide it to you. 23 BY MS. BROWN: 24 Q. Dr. Wolf, did you review the</p>	<p style="text-align: right;">Page 233</p> <p>1 (Deposition Exhibit 14 marked 2 for identification.) 3 MS. O'DELL: Object to the 4 form. 5 (Witness reviews document.) 6 A. You asked me if I reviewed the 7 entire thing as to their opinion. And the 8 answer is yes. And what did you -- 9 BY MS. BROWN: 10 Q. That was the only question. 11 A. That was the only question. 12 Q. All right. And you'll agree on 13 the first page, third paragraph, the FDA 14 concludes that it did not find that the data 15 submitted presented conclusive evidence of a 16 causal association between talc used in the 17 perineal area and ovarian cancer, right? 18 MS. O'DELL: Object to the 19 form. 20 BY MS. BROWN: 21 Q. That's what the FDA said? 22 A. That's what the letter says. 23 Q. That was the FDA's sentence in 24 a letter to the Cancer Prevention Coalition</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 234</p> <p>1 in April of 2014, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And you, Dr. Wolf, disagree</p> <p>4 with that. True?</p> <p>5 A. I do.</p> <p>6 Q. Okay. And so what methodology</p> <p>7 did you employ to distinguish your review of</p> <p>8 the literature from the Food and Drug</p> <p>9 Administration's review?</p> <p>10 A. The first thing is, is that I</p> <p>11 have more literature to support my opinion</p> <p>12 that was not yet available for the FDA.</p> <p>13 Q. And so tell me what that is,</p> <p>14 Doctor.</p> <p>15 A. So all of the -- there are</p> <p>16 three of the case report studies that I have</p> <p>17 referenced in my article: Wu and Cramer and</p> <p>18 Schildkraut. And, in fact, Schildkraut was</p> <p>19 an NCI-sponsored study of African-American</p> <p>20 women and use of talcum powder and risk of</p> <p>21 ovarian cancer. And after it's been</p> <p>22 published, the NCI did update their talcum</p> <p>23 powder on ovarian cancer, to say that this</p> <p>24 study has shown that it increases risk of</p>	<p style="text-align: right;">Page 236</p> <p>1 MS. O'DELL: Excuse me. Object</p> <p>2 to the form. Give me just a minute to</p> <p>3 object. Fair enough. Sorry.</p> <p>4 A. Additionally, the</p> <p>5 meta-analysis, the Penninkilampi study that</p> <p>6 was published in 2017.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. And that didn't include any new</p> <p>9 information, though, right? It's a</p> <p>10 meta-analysis of old data. True?</p> <p>11 A. Of all of the data, some of</p> <p>12 which wasn't available when the FDA wrote</p> <p>13 this letter.</p> <p>14 Q. Sure. But if we're trying to</p> <p>15 identify new data that you, Dr. Wolf, are</p> <p>16 relying on that the FDA didn't have, we have</p> <p>17 three case-control studies and an unpublished</p> <p>18 manuscript by a plaintiffs' expert?</p> <p>19 MS. O'DELL: Object to the --</p> <p>20 excuse me, object to the form,</p> <p>21 misstates her testimony.</p> <p>22 A. There's also two of the three</p> <p>23 cohort studies, the Nurses Health and Women's</p> <p>24 Health Initiative, the Sister Study. The</p>
<p style="text-align: right;">Page 235</p> <p>1 ovarian cancer in African-American women.</p> <p>2 And then the meta-analysis Penninkilampi 2018</p> <p>3 was not available. The recent abstracts and</p> <p>4 now paper from Dr. Saed on causation was not</p> <p>5 available.</p> <p>6 Q. So the three case-control</p> <p>7 studies that you believe distinguish your</p> <p>8 review of the literature from the FDA's are</p> <p>9 Wu 2015, Cramer 2016, and Schildkraut 2016,</p> <p>10 correct?</p> <p>11 A. Yes.</p> <p>12 Q. In addition to a -- is it a</p> <p>13 published paper by Dr. Saed?</p> <p>14 A. It's accepted for publication</p> <p>15 and there's four abstracts.</p> <p>16 Q. Okay. Has it been published</p> <p>17 yet, to your knowledge?</p> <p>18 A. It hasn't yet been published.</p> <p>19 Q. Okay. So in addition to the</p> <p>20 three case-control studies, there is an</p> <p>21 unpublished paper by a plaintiffs' expert in</p> <p>22 the talc litigation, that you say you're</p> <p>23 using to distinguish your review from the</p> <p>24 FDA's review?</p>	<p style="text-align: right;">Page 237</p> <p>1 Women's Health Initiative was published in</p> <p>2 2014, so they wouldn't have had it, likely</p> <p>3 wouldn't have, and the Sister Study.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. And what was the finding as it</p> <p>6 relates to an increased talc use in ovarian</p> <p>7 cancer in the Sister Study?</p> <p>8 A. The Sister Study did not find a</p> <p>9 statistically significant increase, one of</p> <p>10 the issues with all of the three cohort</p> <p>11 studies is none of them are large enough to</p> <p>12 detect a difference and none of them looked</p> <p>13 at use over time.</p> <p>14 Q. Well, we're going to talk about</p> <p>15 that. But you'd agree that the Sister Study</p> <p>16 and the follow-up to the Nurses Health Study</p> <p>17 would not have changed the opinion of the</p> <p>18 FDA, that there's not a causative link twine</p> <p>19 talcum powder and ovarian cancer --</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. -- right?</p> <p>24 A. I'm going to say that</p>

60 (Pages 234 to 237)

Judith K. Wolf, M.D.

Page 238	Page 240
<p>1 indirectly they might have if they had had</p> <p>2 the meta-analysis by Penninkilampi, because</p> <p>3 in that meta-analysis of the cohort studies</p> <p>4 there was a statistical significantly</p> <p>5 increase in serous carcinoma, which is the</p> <p>6 most common type of epithelial ovarian</p> <p>7 cancer, that if you were going to find</p> <p>8 something in those number of women, serous</p> <p>9 would be the most likely that you would find</p> <p>10 a significant increase when they looked at</p> <p>11 all of the cohort studies together.</p> <p>12 Q. Now, of course Wu, the other</p> <p>13 study that you pointed us to, found a greater</p> <p>14 increase in the nonserous cancers, right?</p> <p>15 THE WITNESS: Do you have Wu</p> <p>16 for me to review?</p> <p>17 MS. O'DELL: Yeah.</p> <p>18 A. Yeah, it's not here.</p> <p>19 BY MS. BROWN:</p> <p>20 Q. I'll give you a copy, Doctor.</p> <p>21 So we'll mark Wu as Exhibit 14.</p> <p>22 (Deposition Exhibit 15 marked</p> <p>23 for identification.)</p> <p>24</p>	<p>1 subtype, right? And I'll direct you to Table</p> <p>2 3 for that.</p> <p>3 MS. O'DELL: Just for you to</p> <p>4 orient yourself, Doctor.</p> <p>5 THE WITNESS: Got it.</p> <p>6 A. Which Schildkraut?</p> <p>7 BY MS. BROWN:</p> <p>8 Q. 2016.</p> <p>9 A. 2016.</p> <p>10 MS. BROWN: I'll give you a</p> <p>11 copy right now.</p> <p>12 A. So it does show a --</p> <p>13 significant in nonserous.</p> <p>14 BY MS. BROWN:</p> <p>15 Q. Right. And that's not</p> <p>16 consistent with some of the other studies,</p> <p>17 like Penninkilampi that you were talking</p> <p>18 about earlier, correct?</p> <p>19 A. Well, what I was specifically</p> <p>20 talking about Penninkilampi was the cohort</p> <p>21 studies, finding a statistical significantly</p> <p>22 increase in serous cancers. If you look at</p> <p>23 all of the studies, varying -- often it's</p> <p>24 serous. It doesn't have to be serous. Some</p>
Page 239	Page 241
<p>1 BY MS. BROWN:</p> <p>2 Q. I'll direct you to page 1414,</p> <p>3 which is the "Subgroup Analysis by Histologic</p> <p>4 Type."</p> <p>5 MS. BROWN: Counsel, I have a</p> <p>6 copy for you. Page 1414. I have two,</p> <p>7 actually.</p> <p>8 A. This must not be the right</p> <p>9 paper either. There's no page 1414.</p> <p>10 MS. BROWN: Wrong --</p> <p>11 A. Because there's a couple of</p> <p>12 Wu's.</p> <p>13 BY MS. BROWN:</p> <p>14 Q. Yeah, there's two. We'll</p> <p>15 remark it. This is it. No, this is another</p> <p>16 Wu. I misspoke, Doctor. I meant to point</p> <p>17 you to Schildkraut 2016, which is another</p> <p>18 study that you identified as high quality,</p> <p>19 right?</p> <p>20 A. Yes.</p> <p>21 Q. We'll mark that, as was my</p> <p>22 intention, as 14. And you know one of the</p> <p>23 findings of Schildkraut was a greater</p> <p>24 association with the nonserous histologic</p>	<p>1 of the other studies found an increase in</p> <p>2 endometrioid borderline tumors, other cell</p> <p>3 types of ovarian tumors.</p> <p>4 Q. Is it your opinion, Doctor,</p> <p>5 that talcum powder use perineally increases a</p> <p>6 woman's risk of all different histologic</p> <p>7 types of ovarian cancer?</p> <p>8 A. Well, I'm going to say that</p> <p>9 we're looking at epithelial ovarian cancer,</p> <p>10 and I don't have any evidence that has any</p> <p>11 effect on stromal tumors or dermal cell</p> <p>12 tumors. I think of all of the epithelial</p> <p>13 subtypes, that it's been shown to have -- in</p> <p>14 some studies, in various studies, an increase</p> <p>15 in serous or endometrioid. And the other</p> <p>16 subtypes are usually so small that there's</p> <p>17 probably enough to know statistical</p> <p>18 significance, such as clear cell or mucinous.</p> <p>19 In this study by Schildkraut, it's just</p> <p>20 serous or nonserous. They don't break up the</p> <p>21 other subtypes, at least in this table.</p> <p>22 Q. And the finding of the</p> <p>23 nonserous increased risk is not consistent</p> <p>24 with Penninkilampi's finding on that score,</p>

61 (Pages 238 to 241)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 242</p> <p>1 correct?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. In the cohort studies, it was</p> <p>5 serous. That was statistically significant.</p> <p>6 The two are not -- one does not negate the</p> <p>7 other. What I'm saying is that any of the</p> <p>8 epithelial varying tumors could possibly be</p> <p>9 increased, any cell type. This one shows</p> <p>10 nonserous. The meta-analysis of the cohorts</p> <p>11 showed serous, even though, except for the</p> <p>12 first report of the Nurses Health Study there</p> <p>13 wasn't any statistical increase in the cohort</p> <p>14 studies, one does not negate the other.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. Gates was a follow-up to</p> <p>17 Gertig's --</p> <p>18 A. Gertig -- yeah.</p> <p>19 (Simultaneous discussion</p> <p>20 interrupted by reporter.)</p> <p>21 BY MS. BROWN:</p> <p>22 Q. Gates was a follow-up to --</p> <p>23 A. Gertig --</p> <p>24 MS. O'DELL: If you would let</p>	<p style="text-align: right;">Page 244</p> <p>1 BY MS. BROWN:</p> <p>2 Q. Sure. As a scientist</p> <p>3 evaluating data on cancer, the longer folks</p> <p>4 are studied, the more available information</p> <p>5 there is. True?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. That's true.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. And in evaluating the body of</p> <p>11 literature on talc and ovarian cancer, you</p> <p>12 wouldn't want to close your eyes to some of</p> <p>13 the studies that include additional</p> <p>14 follow-up. True?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. I don't.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. Did you know that Penninkilampi</p> <p>20 does not include the Gates study?</p> <p>21 A. So I'm going to look at that</p> <p>22 paper again to see why he might have left --</p> <p>23 he or she left the Gates study out.</p> <p>24 Q. And for the record, we'll mark</p>
<p style="text-align: right;">Page 243</p> <p>1 her finish and vice versa, I'll do my</p> <p>2 best not to interrupt you.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. Dr. Wolf, Gates was a follow-up</p> <p>5 of the cohort that was followed in the Gertig</p> <p>6 Nurses Health Study, correct?</p> <p>7 A. That's correct.</p> <p>8 Q. And when that cohort was</p> <p>9 followed longer in Gates, there was no</p> <p>10 association with serous cancer, correct?</p> <p>11 A. That's correct.</p> <p>12 Q. And do you agree that it's</p> <p>13 important, when evaluating a body of</p> <p>14 literature, to evaluate all available</p> <p>15 information?</p> <p>16 A. Yes.</p> <p>17 Q. And particularly as it relates</p> <p>18 to the follow-up of individuals who were</p> <p>19 initially studied for perhaps a shorter</p> <p>20 period of time. Fair?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 A. So long-term follow-up is</p> <p>24 always helpful, yes.</p>	<p style="text-align: right;">Page 245</p> <p>1 Penninkilampi as Exhibit 16 your deposition.</p> <p>2 (Deposition Exhibit 16 marked</p> <p>3 for identification.)</p> <p>4 BY MS. BROWN:</p> <p>5 Q. And to help with your review,</p> <p>6 Doctor, if you want to, take as much as you</p> <p>7 need, but page 46 lists the name of the</p> <p>8 studies that are included and Table A was the</p> <p>9 meta-analysis for ever use in ovarian cancer.</p> <p>10 And you agree with me that Gates 2010 is not</p> <p>11 included?</p> <p>12 MS. O'DELL: Feel free to take</p> <p>13 a look at the paper before you answer</p> <p>14 the questions, Doctor.</p> <p>15 A. I see that it was not included.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. And in writing your report and</p> <p>18 identifying Gates as one of the higher</p> <p>19 quality studies, were you aware at the time</p> <p>20 that Gates had omitted the follow-up to the</p> <p>21 Nurses Health Study as published in Gates</p> <p>22 2010?</p> <p>23 MS. O'DELL: Object to the form</p> <p>24 of the question. I don't think that</p>

62 (Pages 242 to 245)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 246</p> <p>1 she referred to Gates as a 2 high-quality study in her report. 3 MS. BROWN: Let me rephrase. 4 That's my fault. 5 BY MS. BROWN: 6 Q. In writing your report and 7 identifying Penninkilampi as one of the 8 higher quality studies, were you aware that 9 Penninkilampi excluded the Gates 2010 10 follow-up to the Nurses Health Study? 11 A. Given that they left it out or 12 they didn't include it, to me it doesn't 13 negate that I think the Penninkilampi study 14 is a good study. I was trying to see if 15 there was a reason why they didn't look at it 16 and I don't see anything mentioned in their 17 methods or in their discussion or their 18 results as to why they did not include it. I 19 still think the Penninkilampi is a good 20 study. 21 Q. Okay. And you are not at all 22 concerned -- would you weigh Penninkilampi 23 less, given the fact that it did not include 24 the most complete data from the Nurses</p>	<p style="text-align: right;">Page 248</p> <p>1 BY MS. BROWN: 2 Q. So your critique of the Berge 3 paper is that there's not a subgroup analysis 4 by histologic type? 5 MS. O'DELL: Object to the 6 form. 7 A. That's -- that wasn't a 8 critique, it's a piece of information. That 9 differently from the Penninkilampi study, 10 which was looking specifically at serous 11 histology of the cohorts, the Berge study 12 didn't look at serous from the cohort 13 separately, they looked at serous overall 14 separately. It's just a difference. It's 15 not a critique. 16 BY MS. BROWN: 17 Q. So one of the things that 18 Penninkilampi looked at was whether ever use 19 of talc increases the risk for ovarian 20 cancer. 21 A. Yes. 22 Q. Do you understand that? 23 A. Yes. 24 Q. And that is the same question</p>
<p style="text-align: right;">Page 247</p> <p>1 Health? 2 MS. O'DELL: Object to form. 3 A. I'm -- I can't answer that 4 question because I don't know what the data 5 would look like if they included the study. 6 BY MS. BROWN: 7 Q. Well, did you review the Berge 8 analysis, the meta-analysis that was done 9 close to the same time? 10 A. Yes. 11 Q. Okay. And were you aware that 12 Berge actually did include Gates as the most 13 recent representation of the Nurses Health 14 cohort? We'll mark the Berge meta-analysis 15 as Exhibit 17. 16 (Deposition Exhibit 17 marked 17 for identification.) 18 (Witness reviews document.) 19 A. So what I don't see in the 20 Berge paper is if they separated out serous 21 for the cohort studies. They looked at 22 serous separately in the study. What I don't 23 see, that they looked at serous histology in 24 the case-control versus the cohorts.</p>	<p style="text-align: right;">Page 249</p> <p>1 that was investigated by Berge, correct? 2 A. Yes. 3 Q. And Penninkilampi excluded the 4 most recent data on the Nurses Health cohort 5 and Berge included it, correct? 6 A. Yes. 7 MS. O'DELL: Object to the 8 form. 9 A. And in ever use of talc in the 10 cohort studies, both of them found no -- 11 nothing, no significant increase. 12 In the Penninkilampi study, 13 which I understand does not include the Gates 14 data, when they looked specifically at the 15 cohort studies, there was a significant 16 increase in serous. 17 In the Berge study when they 18 looked at everything, case-control and 19 cohorts together, there was a significant 20 increase in the risk for serous histology. 21 BY MS. BROWN: 22 Q. I'm sorry, say that last part 23 again, in the -- 24 A. In the Berge study --</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 250</p> <p>1 Q. Uh-huh.</p> <p>2 A. -- what I'm reading here is,</p> <p>3 there is a significant increase in serous</p> <p>4 histology.</p> <p>5 Q. In the case-control studies,</p> <p>6 correct?</p> <p>7 A. I don't see that they separated</p> <p>8 out the case-control studies.</p> <p>9 Q. In reviewing the Berge and</p> <p>10 Penninkilampi meta-analyses, did you pay</p> <p>11 attention to the tests for heterogeneity that</p> <p>12 the authors did in terms of which studies</p> <p>13 could and could not be combined?</p> <p>14 A. In which study are you asking</p> <p>15 me about? I'm sorry. I'm still distracted</p> <p>16 by the Berge one here.</p> <p>17 Q. Do you understand the concept</p> <p>18 of heterogeneity in meta-analysis?</p> <p>19 A. Yes.</p> <p>20 Q. Okay. And so you understand</p> <p>21 that there are certain studies that can --</p> <p>22 because of their study design cannot be</p> <p>23 combined, correct?</p> <p>24 A. Yes.</p>	<p style="text-align: right;">Page 252</p> <p>1 BY MS. BROWN:</p> <p>2 Q. Even though it excludes the</p> <p>3 most recent data from the Nurses Health</p> <p>4 Study. True?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. I specifically chose it because</p> <p>8 it's the most recent one.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. Okay. And you understand that</p> <p>11 the Berge meta-analysis was published at</p> <p>12 right about the same time, right?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. I have to look at the exact</p> <p>16 date.</p> <p>17 MS. BROWN: We need to change</p> <p>18 the tape, so let's go off for a</p> <p>19 second.</p> <p>20 THE VIDEOGRAPHER: Going off</p> <p>21 the record. The time is 2:21 p.m.</p> <p>22 (Recess taken from 2:21 p.m. to</p> <p>23 2:26 p.m.)</p> <p>24 THE VIDEOGRAPHER: This marks</p>
<p style="text-align: right;">Page 251</p> <p>1 Q. And in evaluating the</p> <p>2 Penninkilampi meta-analysis and the Berge</p> <p>3 meta-analysis, did you undertake an effort to</p> <p>4 evaluate the heterogeneity of the studies</p> <p>5 that were combined in those two</p> <p>6 meta-analyses?</p> <p>7 A. And compare the two, is that</p> <p>8 what you're asking me?</p> <p>9 Q. Sure. Here's what I'm after,</p> <p>10 Doctor. I understand that you made a</p> <p>11 determination Penninkilampi is one of the</p> <p>12 more high-quality studies?</p> <p>13 A. Yes.</p> <p>14 Q. And I want to understand your</p> <p>15 methodology in selecting Penninkilampi as a</p> <p>16 higher quality study than Berge.</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 A. So when I look at all of the</p> <p>20 meta-analyses, they all show a significant</p> <p>21 increase in the risk of ovarian cancer with</p> <p>22 minimal use of talcum powder use. I</p> <p>23 specifically chose the Penninkilampi one</p> <p>24 because it was the most recent one.</p>	<p style="text-align: right;">Page 253</p> <p>1 the beginning of disk 3. Back on the</p> <p>2 record. The time is 2:26 p.m.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. Dr. Wolf, before we took a</p> <p>5 break, we were discussing the difference</p> <p>6 between Penninkilampi and the Berge</p> <p>7 meta-analyses. I want to direct your</p> <p>8 attention to page 42 of the Penninkilampi</p> <p>9 article.</p> <p>10 A. That's in this one. Page 42.</p> <p>11 Q. And in the first paragraph on</p> <p>12 the left-hand column, one of the things the</p> <p>13 authors of Penninkilampi note, is that the</p> <p>14 majority of the evidence as it relates to</p> <p>15 perineal talc use in ovarian cancer has come</p> <p>16 from case-control studies, correct?</p> <p>17 MS. O'DELL: Where are you</p> <p>18 reading?</p> <p>19 A. Where are you reading?</p> <p>20 BY MS. BROWN:</p> <p>21 Q. "The evidence for the</p> <p>22 association between perineal talc use and</p> <p>23 ovarian cancer is based on the body of</p> <p>24 knowledge from observational studies and most</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 254</p> <p>1 of these have been retrospective case-control 2 studies prone to recall bias." 3 Do you see that? 4 A. I see that. 5 Q. And do you agree with that, 6 Doctor, that most of the case-control studies 7 that you evaluated and that form the body of 8 epidemiology on talc and ovarian cancer are 9 prone to recall bias? 10 MS. O'DELL: Object to the 11 form. 12 A. I don't agree with that 13 statement. I do agree that one concern of 14 case-control studies is recall bias. I 15 believe that was acknowledged in most, if not 16 all, of the case-control studies and felt not 17 to be an issue. And I looked at that, but 18 the weight of the evidence suggests that most 19 of the studies showed a relationship. 20 Also in a rare disease like 21 ovarian cancer, although a prospective study 22 would be -- might be -- give us more 23 information, the number of women and the 24 amount of time that it would take to do a</p>	<p style="text-align: right;">Page 256</p> <p>1 biostatistician, correct? 2 A. No. 3 Q. Okay. Did you perform a power 4 calculation on any of the studies that you 5 reviewed? 6 A. I did not, but Dr. Narod 7 published a paper where he actually looked at 8 that question and estimated that it would 9 take about 200,000 women to answer the 10 question, and none of these studies have 11 that. 12 Q. And have you calculated how 13 many women were studied in all of the 14 prospective studies and whether or not that 15 was more or less than 200,000? 16 A. Well, if you look at all of 17 them together, putting them together, there 18 are more than 200,000. 19 Q. And did that inform your 20 opinion that the prospective studies -- how 21 did you consider that fact in making the 22 statement that the cohort studies are limited 23 by a lack of power? 24 A. Because each individual study</p>
<p style="text-align: right;">Page 255</p> <p>1 prospective study makes it challenging, and 2 that's one of the challenges with all of the 3 cohort studies. None of them are big enough 4 and most of them are not followed long 5 enough. 6 And so case-control studies are 7 what -- the best way to study a rare disease 8 like this. And given the consistency in the 9 findings, although recall bias can occur, I 10 don't believe it -- after my review of the 11 entire literature, I'm not concerned that 12 recall bias had an effect on the results. 13 BY MS. BROWN: 14 Q. You state in your report on 15 page 8, that all of the cohort studies are 16 limited by lack of power. 17 A. Yes. 18 Q. Is that your opinion? 19 A. Lack of power to ask the 20 specific question, yes. 21 Q. Lack of power to ask? 22 A. To answer the specific 23 question. 24 Q. Okay. And you are not a</p>	<p style="text-align: right;">Page 257</p> <p>1 is limited by lack of power. And two of the 2 three studies are limited by the amount of 3 follow-up and all of the studies are limited 4 by the documentation of how much -- how often 5 and how frequent powder was used. The -- 6 short of the Sister Study, the primary 7 endpoints of the Nurses Health Study and the 8 Women's Health Study were not to look at the 9 relationship of talc and ovarian cancer. It 10 was a secondary add-on study that was done 11 while the studies were ongoing. So they 12 weren't designed to answer that question. 13 Q. Did you consider the published 14 power calculation done by Berge? 15 A. Let me look at Berge's 16 published power calculation. 17 Q. Do you know that -- do you 18 know -- do you recall reviewing that in 19 connection with your -- 20 A. I recall -- 21 Q. -- testimony? 22 A. -- reviewing the paper. I 23 don't recall specifically what his -- his 24 person -- I don't know this person.</p>

65 (Pages 254 to 257)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 258</p> <p>1 Q. I'll direct your attention, 2 then, Doctor, to page 6 of the Berge paper. 3 It looks like you might have a different 4 version than I do, but page 6 of the 5 publication, second column, first paragraph 6 on the -- 7 A. What part of the paper is it 8 in? 9 Q. The discussion section. 10 A. Okay. 11 Q. It's my third paragraph of the 12 discussion section. 13 A. Gotcha. 14 Q. And let me just read this into 15 the record to expedite us here. "An 16 important feature of the present 17 meta-analysis is the inclusion of several 18 cohort studies, which enabled an analysis 19 stratified by study design. This analysis 20 provided evidence of a heterogeneity of 21 results between the two groups of studies 22 with an association generally detected in 23 case-control studies but not in cohort 24 studies. It should be noted that the cohort</p>	<p style="text-align: right;">Page 260</p> <p>1 MS. O'DELL: Excuse me, when 2 you say "here," are you referring to 3 your report? 4 A. In my report, under "Summary of 5 Epidemiological Evidence" on page 8. 6 BY MS. BROWN: 7 Q. And one of the things, Doctor, 8 you provided a site that meta-analyses can be 9 some of the highest form of epidemiological 10 evidence, correct? 11 A. Yes. 12 Q. And the Penninkilampi study 13 that you pointed to was one of the highest -- 14 MS. O'DELL: Why don't we go 15 off the record. 16 MS. BROWN: Let's try to keep 17 going. 18 BY MS. BROWN: 19 Q. The Penninkilampi study that 20 you pointed to as one of the higher quality 21 studies is, in fact, a meta-analysis, 22 correct? 23 A. That's correct. 24 Q. And you are certainly not</p>
<p style="text-align: right;">Page 259</p> <p>1 studies included in the meta-analysis 2 comprised of a total of 429 cases of ovarian 3 cancer exposed to genital talc and 943 4 unexposed: The statistical power of the 5 meta-analysis of these cohort studies to 6 detect a relative risk of 1.25, similar to 7 the result of the meta-analysis of 8 case-control studies, was .99. Thus, low 9 power of cohort studies cannot be invoked as 10 an explanation of the heterogeneity of the 11 results." 12 Did you consider Berge's power 13 calculation when you made the statement in 14 your report, that all of the cohort studies 15 are limited by lack of power? 16 A. My statement is in relationship 17 into each study on their own, not all of them 18 together. And my statement about the lack of 19 power for all over, my opinion about that was 20 based on Narod's paper of needing 200,000 21 women. But this is about -- this is -- this 22 statement here is about each study on their 23 own. None of those studies had 200,000 24 women.</p>	<p style="text-align: right;">Page 261</p> <p>1 meaning to suggest that there's something 2 improper about pooling or combining data in a 3 meta-analysis, correct? 4 MS. O'DELL: Object to the 5 form. 6 A. I don't believe I ever said 7 anything about -- negative about a 8 meta-analysis. 9 BY MS. BROWN: 10 Q. Do you -- did you consider 11 Berge's power calculation of the pooled 12 prospective cohorts when you opined as you 13 did in your report on page 8, that all of the 14 cohort studies are limited by lack of power? 15 MS. O'DELL: Object to the 16 form. 17 A. The two are not comparing the 18 same thing. His power analysis is looking at 19 the pooled analysis. My statement was 20 regarding each individual cohort study on its 21 own. 22 BY MS. BROWN: 23 Q. Do you think there is enough 24 power in the pooled prospective cohorts to</p>

66 (Pages 258 to 261)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 262</p> <p>1 detect a relative risk of 1.25?</p> <p>2 A. I see that Berge says that in</p> <p>3 his discussion. I'm not a statistician. I'd</p> <p>4 have to -- I'm not sure I could answer that</p> <p>5 and I guess I'm going to ask you to -- do you</p> <p>6 think there's enough power in the pooled</p> <p>7 prospective cohorts to detect a relative risk</p> <p>8 of 1.25? I'm going to say possibly. I don't</p> <p>9 know.</p> <p>10 Q. In identifying Penninkilampi as</p> <p>11 one of the higher quality studies, did you do</p> <p>12 an independent verification that the data</p> <p>13 Penninkilampi reports in his article is</p> <p>14 indeed accurate?</p> <p>15 A. Are you -- my understanding of</p> <p>16 what you're asking me is, did I recalculate</p> <p>17 the results? Is that what you're asking me?</p> <p>18 Q. No. I'm asking you, for</p> <p>19 example, on page 46 of Penninkilampi -- we</p> <p>20 have them as exhibits, if that makes it</p> <p>21 easier.</p> <p>22 A. No, I -- okay. Page 46.</p> <p>23 Q. Penninkilampi reports studies,</p> <p>24 a purported odds ratio, a lower limit and an</p>	<p style="text-align: right;">Page 264</p> <p>1 Q. In evaluating the Penninkilampi</p> <p>2 meta-analysis and the Berge analysis, explain</p> <p>3 to me how you weighted both of them.</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. When I was looking at all of</p> <p>7 the meta-analysis, including the Berge and</p> <p>8 the Penninkilampi, to me it -- all of them</p> <p>9 showed a positive correlation between genital</p> <p>10 talcum powder use and ovarian cancer. I</p> <p>11 chose the most recent one to include in my</p> <p>12 report.</p> <p>13 BY MS. BROWN:</p> <p>14 Q. Other than the fact that</p> <p>15 Penninkilampi was the most recent, is there</p> <p>16 any reason -- any other reason you didn't</p> <p>17 include Berge in your report?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. Was there any other reason I</p> <p>21 didn't include Berge?</p> <p>22 BY MS. BROWN:</p> <p>23 Q. Correct.</p> <p>24 A. The reason I chose</p>
<p style="text-align: right;">Page 263</p> <p>1 upper limit. Do you see that?</p> <p>2 A. Yeah.</p> <p>3 Q. Did you go back to the</p> <p>4 individual studies to verify that</p> <p>5 Penninkilampi was correct in that reporting?</p> <p>6 A. Oh, that -- in these charts?</p> <p>7 Q. Correct.</p> <p>8 A. That every -- I did not.</p> <p>9 Q. Would it be important to you in</p> <p>10 determining that a study is of high quality,</p> <p>11 that the authors accurately report the odds</p> <p>12 ratios and the confidence intervals?</p> <p>13 A. It would, but it's not my</p> <p>14 routine or standard for me to go back and</p> <p>15 re-review the odds ratios of every paper to</p> <p>16 confirm that. I would assume that is part of</p> <p>17 the peer-review process that has happened.</p> <p>18 Q. And if there were, in fact,</p> <p>19 errors in the reporting of the odds ratios or</p> <p>20 the confidence intervals, would that call</p> <p>21 into question your reliance on the study?</p> <p>22 A. I would want to see it</p> <p>23 recalculated, if there were -- if there were</p> <p>24 errors.</p>	<p style="text-align: right;">Page 265</p> <p>1 Penninkilampi was because it was the most</p> <p>2 recent. And in my interpretation of the</p> <p>3 meta-analysis, they all show a positive</p> <p>4 correlation, so I just wanted to show the</p> <p>5 most recent.</p> <p>6 Q. And you'll agree with me that</p> <p>7 both meta-analyses -- or the Berge</p> <p>8 meta-analysis shows no increased risk in the</p> <p>9 cohorts, correct?</p> <p>10 A. No increased risk in the</p> <p>11 cohort -- pooled cohorts in the Berge paper.</p> <p>12 Q. And if you consider the Gates</p> <p>13 study as the most recent data available on</p> <p>14 the Nurses Health cohort, you'll agree with</p> <p>15 me there is no evidence at all in the</p> <p>16 prospective cohorts of any increased risk of</p> <p>17 ovarian cancer with talc use. True?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. With the -- the other issues</p> <p>21 with the cohort studies is they ask ever use,</p> <p>22 not current use, length of use, time of use.</p> <p>23 Both the Gates and Gertig and the Houghton,</p> <p>24 the Women's Health Initiative, those studies</p>

67 (Pages 262 to 265)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 266</p> <p>1 were not designed to be able to ask those 2 questions and so we can't have that 3 information. And so the limitations of the 4 cohort studies, as -- as I said before, 5 individually, lack of power, not making the 6 correct queries and short follow-up, except 7 the second follow-up of Gates, but that's 8 only one study and it's still not large 9 enough. 10 BY MS. BROWN: 11 Q. That wasn't my question. My 12 question was, if you consider Gates as the 13 most recent data on the Nurses Health cohort, 14 you would agree with me that there is no 15 evidence in any of the prospective studies 16 that shows a statistically significant 17 increased risk of ovarian cancer with 18 perineal task use. True? 19 MS. O'DELL: Object to the 20 form. 21 A. I would say that all the 22 cohorts or cohort studies have the same 23 limitations, not large enough, not asking the 24 right questions, and the only one that</p>	<p style="text-align: right;">Page 268</p> <p>1 that might get at the answer, two of the 2 three by not being designed to answer that 3 question. And so with those caveats, they 4 saw no statistically significant increase in 5 ovarian cancer with talcum powder use 6 reported as ever use. 7 BY MS. BROWN: 8 Q. What's your methodology for -- 9 do you weight the cohorts and the case 10 controls equally in your analysis? 11 MS. O'DELL: Objection to the 12 form. 13 A. I consider all of the evidence, 14 not only the epidemiologic evidence but the 15 causation evidence, the animal in the in 16 vitro data as a whole and formed my opinion. 17 BY MS. BROWN: 18 Q. My question was, do you weight 19 the case controls equally to the cohorts? 20 MS. O'DELL: Objection, asked 21 and answered. 22 You may answer it. 23 A. I look at the entire evidence, 24 all the epidemiologic evidence, as well as</p>
<p style="text-align: right;">Page 267</p> <p>1 doesn't have the shortest -- short follow-up, 2 which it still may not be long enough, is the 3 Nurses Health Study. And with those caveats, 4 there was no statistically significant 5 increase in ovarian cancer in perineal talcum 6 powder use. But given that ovarian cancer's 7 a rare disease and with those caveats, I'm 8 not sure that they're designed to answer the 9 question. So it doesn't say to me there 10 isn't a risk. 11 BY MS. BROWN: 12 Q. But that wasn't my question. 13 My question was just, there is not a single 14 prospective study that shows an increased 15 risk of ovarian cancer with talcum powder 16 use. That's it. It's yes or no. 17 MS. O'DELL: Excuse me. No, 18 it's not. Objection to form. You may 19 answer it in any way you choose, 20 Dr. Wolf. 21 A. The studies are all limited by 22 lack of power, by short follow-up in two of 23 the three and maybe short follow-up in all 24 three, by not asking the correct questions</p>	<p style="text-align: right;">Page 269</p> <p>1 the in vitro and in vivo evidence and made my 2 decision. 3 BY MS. BROWN: 4 Q. Are you not understanding that 5 question? 6 MS. O'DELL: Counselor, you can 7 ask the questions, but she's given you 8 an answer. Just because you don't 9 like the answer doesn't mean she 10 didn't answer the question. 11 MS. BROWN: I've heard the same 12 answer nine times. The question is -- 13 MS. O'DELL: You're asking the 14 question over and over again. 15 MS. BROWN: You're wasting so 16 much time. 17 BY MS. BROWN: 18 Q. My question really just goes to 19 weight. Okay. I understand you marked at 20 the beginning of the deposition weight of the 21 evidence from UpToDate. Do you remember 22 that? 23 A. Yeah. 24 Q. And my question is just, when</p>

68 (Pages 266 to 269)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 270</p> <p>1 you did this analysis, did you give equal</p> <p>2 weight to the cohorts and the case controls?</p> <p>3 MS. O'DELL: Objection to the</p> <p>4 preamble, which was incorrect, but you</p> <p>5 may answer.</p> <p>6 A. So I weighted every piece of</p> <p>7 evidence not separating by the type of study,</p> <p>8 but looking at the strengths and the</p> <p>9 weaknesses of the study and then together put</p> <p>10 the evidence to make my opinion.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. On page 3 of your report,</p> <p>13 Doctor, you reference the National Cancer</p> <p>14 Institute and that's the public health</p> <p>15 authority's definition of a risk factor. Do</p> <p>16 you remember that?</p> <p>17 A. Yes.</p> <p>18 Q. Fair to say one of the reasons</p> <p>19 you reference the National Cancer Institute</p> <p>20 is that you consider it to be a leading</p> <p>21 public health authority, particularly when it</p> <p>22 comes to cancer?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p style="text-align: right;">Page 272</p> <p>1 it.</p> <p>2 (Deposition Exhibit 18 marked</p> <p>3 for identification.)</p> <p>4 BY MS. BROWN:</p> <p>5 Q. I'm handing you what we've</p> <p>6 marked as Exhibit 18 to your deposition,</p> <p>7 which is a printout from the NCI's website,</p> <p>8 entitled "Ovarian, Fallopian Tube and Primary</p> <p>9 Peritoneal Cancer Prevention, Health</p> <p>10 Professional Version." Do you see that,</p> <p>11 Doctor?</p> <p>12 A. Yes.</p> <p>13 Q. And during your work as a</p> <p>14 gynecologic oncologist, did you look to the</p> <p>15 NCI for information on how to treat your</p> <p>16 patients?</p> <p>17 A. Occasionally, but not</p> <p>18 routinely.</p> <p>19 Q. Do you consider the National</p> <p>20 Cancer Institute to be a reliable source of</p> <p>21 information on cancer epidemiology?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. I consider it a reliable source</p>
<p style="text-align: right;">Page 271</p> <p>1 A. Specifically here, I reference</p> <p>2 the National Cancer Institute because of</p> <p>3 their definition of "associations" versus</p> <p>4 "causative" risk factors.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. And you consider the National</p> <p>7 Cancer Institute to be a leading public</p> <p>8 health authority. True?</p> <p>9 MS. O'DELL: Objection to the</p> <p>10 form, asked and answered.</p> <p>11 A. So if you're asking me -- what</p> <p>12 I think I hear you asking me is why did I</p> <p>13 reference the National Cancer Institute here,</p> <p>14 and I referenced it because of this</p> <p>15 definition.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. The National Cancer Institute</p> <p>18 has reviewed the epidemiology on talc and</p> <p>19 ovarian cancer, correct?</p> <p>20 A. That's correct.</p> <p>21 Q. Did you consider the National</p> <p>22 Cancer Institute's review of the epidemiology</p> <p>23 in forming your opinions in this case?</p> <p>24 A. I read it and I did consider</p>	<p style="text-align: right;">Page 273</p> <p>1 on cancer as a whole. And again, to me</p> <p>2 it's -- it's one of the pieces of evidence</p> <p>3 that I might look to to find some</p> <p>4 information.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. And what the National Cancer</p> <p>7 Institute has done here is evaluate risk</p> <p>8 factors for ovarian cancer, correct?</p> <p>9 A. Yes.</p> <p>10 Q. And, for example, if you look</p> <p>11 at page 3 of 21, the National Cancer</p> <p>12 Institute's information begins with factors</p> <p>13 with adequate evidence of an increased risk</p> <p>14 of ovarian cancer, correct?</p> <p>15 A. Yes.</p> <p>16 Q. Okay. And they list things</p> <p>17 like endometriosis, correct?</p> <p>18 A. Yeah.</p> <p>19 Q. They list hormone replacement</p> <p>20 therapy. True?</p> <p>21 A. Yes.</p> <p>22 Q. And the National Cancer</p> <p>23 Institute goes on -- and one of the things</p> <p>24 they do not list as a factor with adequate</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 274</p> <p>1 evidence of an increased risk is talcum 2 powder use, correct? 3 A. That's correct. 4 Q. And what the National Cancer 5 Institute does, is it identifies some area 6 where there's uncertainty in terms of a risk 7 factor, right? 8 A. Yes. 9 Q. And so on page 7 of 21, for 10 example, they identify infertility treatment 11 as an area of uncertainty, correct? 12 A. Yes. 13 Q. And when it comes to perineal 14 talc use, however, the National Cancer 15 Institute has determined that that is a 16 factor with inadequate evidence of an 17 association of the risk of ovarian cancer, 18 correct? 19 MS. O'DELL: Object to the 20 form. 21 A. That's where they placed it in 22 this, yes. 23 BY MS. BROWN: 24 Q. And directing your attention to</p>	<p style="text-align: right;">Page 276</p> <p>1 BY MS. BROWN: 2 Q. Let's reorient ourselves now 3 that we're all on the same page. The 4 National Cancer Institute has classified 5 perineal talc exposure as a factor with 6 inadequate evidence of an association with 7 ovarian cancer, correct? 8 MS. O'DELL: Object to the 9 form. 10 A. It's listed under factors with 11 inadequate evidence, that's correct. 12 BY MS. BROWN: 13 Q. All right. And the National 14 Cancer Institute has factors with adequate 15 evidence, right? 16 A. Yes. 17 Q. We just looked at some. 18 A. Yes. 19 Q. It has factors with uncertain 20 evidence, right? 21 A. Yes. 22 Q. And then it has factors with 23 inadequate evidence, and that includes 24 perineal talc exposure, correct?</p>
<p style="text-align: right;">Page 275</p> <p>1 page 14 of 21, what the National Cancer 2 Institute has concluded is that, "The weight 3 of the evidence does not support an 4 association between perineal talc exposure 5 and an increased risk of ovarian cancer. 6 Results from case-control and cohort studies 7 are inconsistent." 8 Do you see that? 9 MS. O'DELL: Object to the 10 form. Can I just ask where you're 11 reading from? You said page 21. 12 A. Yeah, I don't see that. 13 BY MS. BROWN: 14 Q. Page 14 of 21. 15 MS. O'DELL: We don't have 21. 16 We have 18 pages. 17 A. And page 14 is references. 18 BY MS. BROWN: 19 Q. You have a different version 20 than I do. I'll get you there. Right here, 21 perineal talc exposure. 22 MS. O'DELL: So repeat the 23 question, please. 24 MS. BROWN: Sure.</p>	<p style="text-align: right;">Page 277</p> <p>1 A. That's correct. 2 MS. O'DELL: Object to the 3 form. 4 BY MS. BROWN: 5 Q. And what the National Cancer 6 Institute has determined here is that the 7 weight of the evidence does not support an 8 association between perineal talc exposure 9 and an increased risk of ovarian cancer. 10 A. That's the part I don't -- 11 Q. Results -- 12 A. That's where I'm trying to find 13 -- 14 Q. Let me read it and then I'm 15 going to help you. 16 "Results from case-control and 17 cohort studies are inconsistent." And what 18 I'm reading are the first two lines of the 19 perineal talc exposure section. 20 A. Okay. Okay. What's your 21 question? 22 Q. You, Dr. Wolf, disagree with 23 the National Cancer Institute, correct? 24 A. In this instance, I do.</p>

70 (Pages 274 to 277)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 278</p> <p>1 Q. And tell me what methodology 2 you have employed that is different from the 3 weight of the evidence approach, referenced 4 here by the National Cancer Institute. 5 A. So I see that the National 6 Cancer Institute has referenced five 7 articles. So one of the things is that I 8 believe that my review of the entire body of 9 literature is much broader than five 10 articles. And when I look at the most recent 11 article, they do have one article from 2016, 12 which is the Schildkraut data, which is -- 13 they just now at the end of 2018, added that 14 data into theirs. So I would say there's 15 other data that they either didn't have when 16 they did the review or didn't include when 17 they did the review. 18 Q. And in offering that opinion, 19 have you considered, Doctor, that according 20 to this document from the NCI, board members 21 meet monthly to review recently published 22 articles? I'll point you to the section 23 entitled "About This PDQ Summary," at the 24 very end, under the section "Reviewers and</p>	<p style="text-align: right;">Page 280</p> <p>1 opinion. It's my experience that in order to 2 get someone like the National Cancer 3 Institute or some other guideline to suggest 4 something, there's generally a lag of several 5 years between publication of all the 6 literature and when the committee changes 7 something. An example of that is that the 8 Schildkraut paper was published in 2016. It 9 wasn't until the -- end of 2018 that they 10 included it. 11 Q. Dr. Wolf, are you aware of any 12 public health authority that has concluded 13 talcum powder causes ovarian cancer? 14 MS. O'DELL: Object to the 15 form. 16 A. I'm aware that IARC has 17 considered that talc is possibly 18 carcinogenic, that asbestos is carcinogenic. 19 BY MS. BROWN: 20 Q. IARC has not concluded that 21 talc causes ovarian cancer, correct? 22 MS. O'DELL: Object to the 23 form. 24 A. One of the reasons for the</p>
<p style="text-align: right;">Page 279</p> <p>1 Updates," do you see the National Cancer 2 Institute's -- 3 A. I see that. 4 Q. -- board members meeting 5 monthly to review recently published 6 articles, right? 7 A. Yes. 8 MS. O'DELL: Object to the 9 form. 10 BY MS. BROWN: 11 Q. And we see at the very last 12 page, that this particular document was 13 updated a few weeks ago in December 21st of 14 2018? 15 A. Yes. 16 Q. Okay. Do you have any other 17 scientific evidence or methodology that would 18 distinguish your review of the literature 19 from the folks at the National Cancer 20 Institute? 21 A. I'm going to go back to the 22 review of the entire body of the literature. 23 I don't know which articles they look at once 24 a month to make a determination with their</p>	<p style="text-align: right;">Page 281</p> <p>1 review of talc was the concern of ovarian 2 cancer. The fact that they have considered 3 it possibly carcinogenic, to me is an 4 indication that they think it's possibly 5 carcinogenic. 6 BY MS. BROWN: 7 Q. Okay. Let's break that up. 8 Are you aware of any public health authority 9 that agrees with your opinion that talcum 10 powder causes ovarian cancer? 11 MS. O'DELL: Object to the 12 form. 13 A. When I formed my opinion, I 14 looked at all of the data that was available 15 to me, including the data as recent as 16 December. The Canada health assessment, the 17 Taher paper. And I believe that my opinion 18 is based on a greater weight of the evidence 19 than the review of the National Cancer 20 Institute or anything that was available 21 prior to this for a body to review. And if I 22 go back to the talc and IARC study, even with 23 papers only till 2007 and 2008, there was 24 enough evidence that they thought that talc</p>

Judith K. Wolf, M.D.

Page 282	Page 284
<p>1 was possibly carcinogenic.</p> <p>2 BY MS. BROWN:</p> <p>3 Q. IARC did not consider three of</p> <p>4 the four prospective cohort studies that</p> <p>5 showed no increased risk of with talcum</p> <p>6 powder, true?</p> <p>7 A. They also did not show --</p> <p>8 include any paper that was published after</p> <p>9 2007.</p> <p>10 Q. And that would include three of</p> <p>11 the four prospective cohort studies that</p> <p>12 showed no risk, right?</p> <p>13 A. That would include anything</p> <p>14 published after 2007.</p> <p>15 Q. And as I understand your</p> <p>16 testimony as it relates to the National</p> <p>17 Cancer Institute, you believe that despite</p> <p>18 the fact that the NCI updated its position as</p> <p>19 recently as a few weeks ago, they have not</p> <p>20 reviewed the most latest literature. Is that</p> <p>21 your testimony?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. I'm saying that I don't know if</p>	<p>1 correct?</p> <p>2 A. Yes.</p> <p>3 Q. And IARC has and done -- has</p> <p>4 and does make that determination as it</p> <p>5 relates to certain substances, correct?</p> <p>6 A. Yes.</p> <p>7 Q. Okay. IARC has not determined</p> <p>8 that nonasbestiform talc is -- strike that.</p> <p>9 IARC has not determined that</p> <p>10 there is sufficient evidence that</p> <p>11 nonasbestiform talc causes ovarian cancer,</p> <p>12 correct?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. In the IARC opinion on talc,</p> <p>16 platy talc, what was assumed to be platy talc</p> <p>17 without any fibrous contamination, the score</p> <p>18 was 2B, which is possibly carcinogenic.</p> <p>19 BY MS. BROWN:</p> <p>20 Q. And in explaining what IARC</p> <p>21 means by "possibly carcinogenic," IARC</p> <p>22 explains that chance, bias or confounding</p> <p>23 can't be ruled out with reasonable</p> <p>24 confidence, correct?</p>
Page 283	Page 285
<p>1 they have. The most recent literature that</p> <p>2 they cited is two years old.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. And what literature do you</p> <p>5 think has come out in the next -- in the last</p> <p>6 two years that IARC -- excuse me, that NCI,</p> <p>7 despite a publication last month, did not</p> <p>8 cite?</p> <p>9 A. Well, I'm going to say both the</p> <p>10 Berge meta-analysis and the Penninkilampi</p> <p>11 meta-analysis.</p> <p>12 Q. IARC has a classification for</p> <p>13 agents that it believes to be carcinogenic,</p> <p>14 correct?</p> <p>15 A. Yes.</p> <p>16 Q. And that is a group 1, correct?</p> <p>17 A. That's correct.</p> <p>18 Q. And IARC has and does make a</p> <p>19 determination that with some substances,</p> <p>20 there is sufficient evidence of</p> <p>21 carcinogenicity. True?</p> <p>22 A. That's correct.</p> <p>23 Q. And IARC does have a category</p> <p>24 that an agent may be probably carcinogenic,</p>	<p>1 A. That's correct.</p> <p>2 Q. And you think as it relates to</p> <p>3 IARC's interpretation of epidemiology,</p> <p>4 they're wrong, right?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. I think that they made the</p> <p>8 decision that they thought was correct with</p> <p>9 the information that they had at the time</p> <p>10 that they made it.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. At the time that IARC</p> <p>13 determined that talc -- nonasbestiform talc</p> <p>14 had limited evidence of carcinogenic, you</p> <p>15 believe that was correct?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. I'm going to say again what I</p> <p>19 said the last time. That I believe that they</p> <p>20 came to that conclusion based on their review</p> <p>21 of the literature that they had at the time.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. And you understand when IARC</p> <p>24 does a literature review, it employs the</p>

72 (Pages 282 to 285)

Judith K. Wolf, M.D.

Page 286	Page 288
<p>1 Bradford Hill criteria?</p> <p>2 A. Yes.</p> <p>3 Q. And is that the criteria you</p> <p>4 evaluated the literature with here too?</p> <p>5 A. I actually -- I didn't know</p> <p>6 that's what I was doing until I read the</p> <p>7 Bradford Hill criteria paper myself and</p> <p>8 realized that that's what I do when I review</p> <p>9 the literature and it fit very nicely into</p> <p>10 that criteria. So in my report, yes.</p> <p>11 Q. As a practicing gynecologic</p> <p>12 oncologist, you don't use the epidemiologic</p> <p>13 tool of Bradford Hill criteria; is that fair?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. In my general practice, I don't</p> <p>17 use the Bradford Hill criteria, specifically</p> <p>18 calling it that, but all of those criteria</p> <p>19 are what I use when I evaluate something.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. And you understand that when</p> <p>22 the scientists at IARC evaluate whether or</p> <p>23 not a substance is carcinogenic, they too</p> <p>24 employ the Bradford Hill criteria, correct?</p>	<p>1 right?</p> <p>2 A. Yes.</p> <p>3 Q. Okay. There had been prior</p> <p>4 case-control studies in that same relative</p> <p>5 risk range, correct?</p> <p>6 A. Yes.</p> <p>7 Q. Okay. There was nothing new or</p> <p>8 different about the relative risks shown in</p> <p>9 the most recent case-control studies,</p> <p>10 correct?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. There was additional -- it's</p> <p>14 just confirmation and -- of the same</p> <p>15 information, showing consistency, which is</p> <p>16 one of the tenets of the Bradford Hill</p> <p>17 criteria.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. And, in fact, there's no</p> <p>20 consistency with the findings of the</p> <p>21 prospective studies, right?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. The three cohort studies, I'll</p>
Page 287	Page 289
<p>1 A. Yes.</p> <p>2 Q. Okay. Is there something</p> <p>3 different in your mind, about how you</p> <p>4 employed Bradford Hill and how IARC employed</p> <p>5 Bradford Hill?</p> <p>6 A. We had different information.</p> <p>7 Q. And the different information</p> <p>8 you're referring to are some additional</p> <p>9 case-control studies and additional</p> <p>10 meta-analysis?</p> <p>11 A. And cohort studies and in</p> <p>12 inflammatory papers, causation papers that</p> <p>13 weren't published before 2007.</p> <p>14 Q. And you would agree with me</p> <p>15 that --</p> <p>16 MS. O'DELL: Excuse me,</p> <p>17 published before 2007?</p> <p>18 THE WITNESS: Were not. Were</p> <p>19 not.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. You would agree with me that</p> <p>22 the general relative risks seen in the</p> <p>23 additional case-control studies that you're</p> <p>24 referring to, range from about 1.2 to 1.6,</p>	<p>1 say once again, had limitations which I don't</p> <p>2 think allowed us to answer the question about</p> <p>3 talc and ovarian cancer, the size, the</p> <p>4 information about use and the follow-up.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. In your review of the</p> <p>7 literature, did you make the determination</p> <p>8 that the case-control studies asked different</p> <p>9 questions about use than the prospective</p> <p>10 studies?</p> <p>11 A. The case-control studies, many</p> <p>12 of them, asked more specific questions and</p> <p>13 were able to obtain more information.</p> <p>14 Q. Is it -- you state in your</p> <p>15 report that the case-control studies are</p> <p>16 consistent, right?</p> <p>17 A. Yes.</p> <p>18 Q. And they are not -- when you</p> <p>19 look at the case-control studies and the</p> <p>20 cohort studies, though, there is not</p> <p>21 consistency, correct?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. When I look at the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 290</p> <p>1 epidemiologic data as a whole, as well as all 2 of the rest of the data about causation and 3 the makeup and the chemicals -- the 4 components of talcum powder product, it's 5 all -- it's consistent to me, the weight of 6 the evidence is consistent. 7 BY MS. BROWN: 8 Q. Prospective studies have not 9 found an increased risk, correct? 10 MS. O'DELL: Object to the 11 form. 12 A. Prospective studies have 13 limitations, which I have described multiple 14 times, size, follow-up, length of follow-up, 15 information about talc use. And given those 16 caveats, they have not shown a statistical 17 increase -- significant increase in ovarian 18 cancer. 19 BY MS. BROWN: 20 Q. And you state that -- in your 21 report at page 6, "Overall, the case-control 22 studies are consistent showing a 30-50 23 percent increase in risk of ovarian cancer 24 with talcum powder use."</p>	<p style="text-align: right;">Page 292</p> <p>1 BY MS. BROWN: 2 Q. One of the studies you pointed 3 us to as a high quality study was the Wu 4 study, right? 5 A. Yes. 6 Q. And one of the things that's 7 reported in the Wu study and that you know as 8 a practicing gynecological oncologist, is 9 that the incident rate of ovarian cancer is 10 much lower in African-American women than it 11 is in Whites, correct? 12 A. That's correct. 13 Q. And one of the things that Wu 14 reports is that talcum powder use is much 15 higher in African-American women than in 16 Whites, correct? 17 A. That's correct. 18 Q. And how do you reconcile those 19 two facts, Doctor, that the population that 20 has the highest use of talcum powder has the 21 lowest incidence of ovarian cancer? 22 A. Well, if we could pull up the 23 Wu study, I don't recall how many 24 African-American women were in that study,</p>
<p style="text-align: right;">Page 291</p> <p>1 Do you see that? 2 A. Yes. 3 Q. Okay. And are you referring to 4 ever use and ovarian cancer? 5 A. I'm referring to however it was 6 reported in the case-control studies. 7 Q. Have you done an analysis of 8 the case-control studies to see what the 9 finding is when the same question is asked? 10 A. So I, personally, haven't. 11 That's where I point to the meta-analysis, to 12 look at specific questions about how -- which 13 questions were asked. 14 Q. And are you aware that when you 15 look at the ever used question in the 16 case-control studies, the majority of those 17 studies do not show an increased risk? 18 MS. O'DELL: Object to the 19 form. 20 A. Which is one of the limitations 21 of prospective studies because they only 22 asked ever used without details about how 23 often, how frequent, how long. 24</p>	<p style="text-align: right;">Page 293</p> <p>1 but the number was, I believe, small. 2 Q. Well, wasn't this one of the 3 studies you identified as being particularly 4 high quality? 5 A. Yes. 6 Q. Okay. 7 A. Just because it didn't have a 8 lot of African-American patients doesn't make 9 it -- doesn't make it not a good study; it's 10 just a fact. 11 Q. But your critique of the cohort 12 studies is that they didn't have enough 13 people, right? 14 A. For a primary analysis. This 15 is a secondary point of African-Americans. 16 When you look at the Schildkraut study, which 17 was specifically for African-Americans, there 18 was a significant increase. 19 Q. The primary focus of the Wu 20 paper was whether African-American women had 21 an increased risk of talcum powder use. 22 A. This is not the right Wu paper. 23 MS. O'DELL: Let me get it for 24 you.</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 294</p> <p>1 THE WITNESS: I don't have the</p> <p>2 right Wu paper.</p> <p>3 MS. O'DELL: Just a second</p> <p>4 here.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. Is that what you're looking</p> <p>7 for, Doctor? We can mark it.</p> <p>8 A. Yes, this is the one.</p> <p>9 MS. O'DELL: Thank you.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Let me just stick 19 on that</p> <p>12 for you.</p> <p>13 (Deposition Exhibit 19 marked</p> <p>14 for identification.)</p> <p>15 BY MS. BROWN:</p> <p>16 Q. Doctor, I have marked for the</p> <p>17 record as Exhibit 19, the Wu article we've</p> <p>18 been discussing. And my question for you</p> <p>19 here is how -- what methodology you employed</p> <p>20 to reconcile some of the facts that are</p> <p>21 reported in Wu; namely, that African-American</p> <p>22 women had the lowest incidence of ovarian</p> <p>23 cancer and the highest incidence of talcum</p> <p>24 powder use?</p>	<p style="text-align: right;">Page 296</p> <p>1 how many were African-American. There were</p> <p>2 128.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. 1700? Are you looking at Wu?</p> <p>5 A. Yes.</p> <p>6 MS. O'DELL: Her testimony was</p> <p>7 not -- was 128.</p> <p>8 A. 128 African-Americans.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. I misheard you.</p> <p>11 A. 1700 women total. Of those,</p> <p>12 128 were African-American, most of them were</p> <p>13 non-Hispanic/White. So that study isn't</p> <p>14 powered to answer the question about</p> <p>15 African-Americans and the relationship of</p> <p>16 talcum powder and ovarian cancer. It's not</p> <p>17 enough.</p> <p>18 Q. We're missing each other. I</p> <p>19 want you to put this study aside. I'm asking</p> <p>20 you a question about facts that are reported</p> <p>21 here that you know as a gynecologic</p> <p>22 oncologist. One of the those facts, you'll</p> <p>23 agree with me, is that African-American women</p> <p>24 have a lower incidence of ovarian cancer than</p>
<p style="text-align: right;">Page 295</p> <p>1 A. So the title of the Wu paper</p> <p>2 says, "African-Americans and Hispanics Remain</p> <p>3 at Lower Risk of Ovarian Cancer," but when</p> <p>4 you read the purpose of this study, it was to</p> <p>5 elucidate risk factors for disease and to</p> <p>6 evaluate differences across -- across</p> <p>7 Hispanics.</p> <p>8 Q. Sure.</p> <p>9 A. But not specifically</p> <p>10 African-Americans.</p> <p>11 Q. No, Doctor, I'm using the</p> <p>12 information reported in this study that you</p> <p>13 identified as high quality to pose a</p> <p>14 commonsense question for you. Which is that,</p> <p>15 how do you reconcile the idea that the</p> <p>16 population that has the lowest amount of</p> <p>17 ovarian cancer has the highest amount of</p> <p>18 powder use?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form. She's answered your question</p> <p>21 previously.</p> <p>22 But you may respond.</p> <p>23 A. So the reason I wanted to look</p> <p>24 at this paper was to see, of the 1700 women,</p>	<p style="text-align: right;">Page 297</p> <p>1 white women, right?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. Yes.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. Okay. And one of the things</p> <p>7 you know from reading Wu, because they report</p> <p>8 it, is that African-American women are</p> <p>9 traditionally higher talcum powder users than</p> <p>10 white women, right?</p> <p>11 A. Yes.</p> <p>12 Q. And so what methodology have</p> <p>13 you employed in opining that talcum powder</p> <p>14 causes ovarian cancer to explain this</p> <p>15 difference?</p> <p>16 A. Because when I look at the</p> <p>17 Schildkraut study, which was a larger study</p> <p>18 of African-American women, I believe, I have</p> <p>19 to look at the numbers, there was a</p> <p>20 statistical significant difference increase</p> <p>21 in ovarian cancer in women --</p> <p>22 African-American women.</p> <p>23 Q. Right. But you know the annual</p> <p>24 incidence of ovarian cancer in</p>

75 (Pages 294 to 297)

Judith K. Wolf, M.D.

Page 298	Page 300
<p>1 African-American women is historically and 2 remains much lower? 3 A. Yes. 4 MS. O'DELL: Objection, form, 5 asked and answered. 6 BY MS. BROWN: 7 Q. I mean, do you understand what 8 I'm saying here? How do you reconcile that? 9 If talcum powder use really did cause ovarian 10 cancer, why is the population that uses 11 talcum powder the most, the population that 12 gets ovarian cancer the least? 13 MS. O'DELL: Objection to the 14 form, asked and answered. 15 You may answer. 16 A. Okay. So there are multiple 17 risk factors for ovarian cancer. If 18 African-American women have some protection 19 from getting ovarian cancer, for whatever 20 reason they don't get it as often, it doesn't 21 matter what the risk factor is. If you look 22 at an individual risk factor in that 23 population alone and it increases their risk 24 over their baseline, it's a risk factor.</p>	<p>1 MS. BROWN: Your objection is 2 to form. 3 MS. O'DELL: Fine. I think 4 Judge Pisano would understand my 5 objection. And what I've objected to 6 is the fact that you've asked the same 7 question ten times, often with facial 8 expressions, with gestures toward the 9 witness, which is inappropriate under 10 the protocol. But I'm not being 11 critical of that. I'm pointing it out 12 for the record. So if you've got a 13 question, ask it, the doctor will 14 answer it to the best of her ability 15 as she's been doing. But to keep 16 berating the witness with the same 17 question is really not appropriate. 18 MS. BROWN: Counsel, your 19 objection under the Federal Rules is 20 to form. If there's something you'd 21 like to discuss off the record, I'd be 22 happy to do that. We need to move on 23 here. We're wasting a lot of time. 24 If Dr. Wolf would answer the question,</p>
Page 299	Page 301
<p>1 BY MS. BROWN: 2 Q. What methodology have you 3 employed to explain the fact that a 4 population that uses this product the most 5 gets ovarian cancer the least? How do you 6 reconcile that? 7 MS. O'DELL: Objection, asked 8 and answered. You've asked the same 9 question ten times. The doctor -- 10 MS. BROWN: When I get an 11 answer, I'll be happy to move on. 12 MS. O'DELL: Excuse me, I'm 13 not -- you want an answer you want. 14 She's given you an answer to the 15 question. 16 MS. BROWN: Counsel, form. 17 MS. O'DELL: Let me finish. 18 MS. BROWN: But it's form. 19 Federal Rules. 20 MS. O'DELL: I can say what I'm 21 going to say. 22 MS. BROWN: Well, we can get 23 the judge. 24 MS. O'DELL: Fine.</p>	<p>1 I would be happy to move on. 2 MS. O'DELL: She's answered 3 your question. 4 You may answer it again -- 5 BY MS. BROWN: 6 Q. Please answer it again, 7 Dr. Wolf. 8 MS. O'DELL: -- Dr. Wolf, and 9 feel free to give the same answer if 10 it's the same answer. 11 A. My understanding of your 12 question is, how do -- how do I -- given that 13 African-American women are less likely to get 14 ovarian cancer and given that they use more 15 talcum powder, why don't we see more ovarian 16 cancer from talcum powder in African-American 17 women? Is that what you're asking? 18 BY MS. BROWN: 19 Q. No, Doctor. Have you 20 considered that as a factor that your opinion 21 might not be right? 22 MS. O'DELL: Object to the 23 form. 24 A. My opinion is based on a study</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 302</p> <p>1 of African-American women who use or did not 2 use talcum powder and ovarian cancer in the 3 case-control study of Schildkraut, which was 4 the most recent paper mentioned in the NCI 5 update on talc and ovarian cancer. 6 BY MS. BROWN: 7 Q. And do you have Schildkraut in 8 front of you? We marked it as Exhibit 19. 9 A. I have it. 10 Q. 15, I'm sorry. One of the 11 things that Schildkraut attempted to address 12 was recall bias as a result of talcum powder 13 lawsuits, correct? 14 MS. O'DELL: Object to the 15 form. 16 BY MS. BROWN: 17 Q. And I'll direct you, Doctor, 18 to -- 19 A. Because I'm looking at the 20 primary endpoint of the study and the primary 21 endpoint of the study was to analyze the 22 relationship of genital powder and nongenital 23 powder exposure in African-American women in 24 a case-control study of invasive ovarian</p>	<p style="text-align: right;">Page 304</p> <p>1 Schildkraut endeavored to do was to determine 2 whether the class action lawsuits in 2014 3 created recall bias in the women who were 4 diagnosed with ovarian cancer? 5 A. Okay. 6 MS. O'DELL: Object to the 7 form. 8 BY MS. BROWN: 9 Q. Do you recall that? 10 A. I do. 11 Q. And do you think that that is 12 an important thing for an author of a 13 case-control study to analyze? 14 A. I do. 15 Q. And you recall that when 16 Schildkraut analyzed folks who had been 17 interviewed prior to the lawsuits in 2014 and 18 after the lawsuits in 2014, there was a 19 significant difference in the number of 20 people diagnosed with ovarian cancer who 21 reported talcum powder use. Do you remember 22 that? 23 A. Well, I'm looking for that -- I 24 see in the query in the table, but I don't</p>
<p style="text-align: right;">Page 303</p> <p>1 cancer -- epithelial ovarian cancer in 2 African-American women. 3 Q. In forming your opinions in 4 this case, did you consider the subgroup 5 analysis that Schildkraut conducted on women 6 who were interviewed before and after the 7 class action lawsuits began in 2014? 8 MS. O'DELL: Objection to form. 9 A. I'm looking for those results 10 in the paper. 11 BY MS. BROWN: 12 Q. In forming your opinion in the 13 case, did you consider those? 14 MS. O'DELL: Object to the 15 form. 16 A. I need to remind myself what 17 those results were. 18 BY MS. BROWN: 19 Q. Okay. I'll direct you to Table 20 2 of the paper, which in my copy is 1414. 21 A. I see that. And what was your 22 question? 23 Q. Do you recall, based on your 24 review of this paper, that one of the things</p>	<p style="text-align: right;">Page 305</p> <p>1 see a statistical significant difference, and 2 that's what I'm looking for in the results, 3 and I don't see it. If you know where it is, 4 you can point it out to me. 5 Q. Here's what I want to ask you 6 about. In two thousand -- you looked at this 7 table, right, you considered this subgroup 8 analysis? 9 A. Yes. 10 Q. Because you would agree with 11 Schildkraut, that recall bias, particularly 12 where there's been a lot of lawsuit 13 attention, is important to investigate, 14 correct? 15 MS. O'DELL: Object to the 16 form. 17 A. Recall bias is always something 18 to investigate. 19 BY MS. BROWN: 20 Q. But it's -- it could be 21 particularly acute in the context of a lot of 22 media attention due to lawsuits, right? 23 MS. O'DELL: Object to the 24 form.</p>

77 (Pages 302 to 305)

Judith K. Wolf, M.D.

Page 306	Page 308
<p>1 A. Something to look at.</p> <p>2 BY MS. BROWN:</p> <p>3 Q. And one of the things</p> <p>4 Schildkraut actually did in its analysis, was</p> <p>5 it controlled for the recall bias -- it tried</p> <p>6 to control for that recall bias, right?</p> <p>7 A. Well, it looked at it, yes.</p> <p>8 Q. And the reason it felt it had</p> <p>9 to control -- he felt -- she felt she had to</p> <p>10 control for it was because she found a</p> <p>11 statistically significant effect modification</p> <p>12 by year of interview, right?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. And that conclusion is at the</p> <p>17 end of the results -- second paragraph of the</p> <p>18 results on page 1413. Do you recall</p> <p>19 reviewing that?</p> <p>20 A. I don't see anything that says</p> <p>21 about the year of -- year of review.</p> <p>22 Q. The second paragraph in the</p> <p>23 results section of the paper concludes, "A</p> <p>24 test for effect modification by year of</p>	<p>1 A. What I'm reading, it says, "In</p> <p>2 2014 and later, we observed an increase in</p> <p>3 any powder use. Although increased, these</p> <p>4 exposure prevalences were not statistically</p> <p>5 significant for those interviewed before</p> <p>6 2014."</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Did you consider the author's</p> <p>9 conclusion that there was a statistically</p> <p>10 significant effect modification by year of</p> <p>11 interview when you reviewed this paper?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. Yes. But -- yes, but this does</p> <p>15 not clarify why that would be, because there</p> <p>16 was no statistical difference in reported</p> <p>17 use.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. And what happened, Doctor, if</p> <p>20 you look at Table 2, is that prior to --</p> <p>21 those folks who were interviewed about</p> <p>22 whether or not they had used powder before</p> <p>23 2014, 34 percent of the controls reported it</p> <p>24 and about 36 and a half percent of the cases</p>
Page 307	Page 309
<p>1 interview was statistically significant with</p> <p>2 P equaling 0.005."</p> <p>3 Do you see that?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. Okay. "Although increased,</p> <p>7 exposure prevalences were not significantly</p> <p>8 different from those interviewed before</p> <p>9 2014."</p> <p>10 So the exposure was no</p> <p>11 different.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. Well, it was and the authors</p> <p>14 concluded that they couldn't rule it out as</p> <p>15 inflating the odds ratios, didn't they?</p> <p>16 MS. O'DELL: Objection, form.</p> <p>17 A. It was not statistically</p> <p>18 different.</p> <p>19 BY MS. BROWN:</p> <p>20 Q. They found a statistically</p> <p>21 significant effect modification. Do you see</p> <p>22 that conclusion?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p>1 reported it, right?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. Do you see me --</p> <p>6 A. I see that.</p> <p>7 Q. And then when they stratified</p> <p>8 by interview date and they asked people after</p> <p>9 the lawsuits if they had used powder, the</p> <p>10 folks who did not get ovarian cancer reported</p> <p>11 it at about the same percentage, right, 34.4</p> <p>12 percent?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. Yes, 30 and 42 percent.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. Well, 34 and 34.4.</p> <p>18 A. Oh, I'm sorry. After --</p> <p>19 Q. You see that? Any genital use.</p> <p>20 A. Yes.</p> <p>21 Q. Okay. So 34 percent of people</p> <p>22 who did not have ovarian cancer reported talc</p> <p>23 use before 2014, right? And 34.4 percent of</p> <p>24 people who did not have ovarian cancer</p>

Judith K. Wolf, M.D.

Page 310	Page 312
<p>1 reported talc use after 2014, right?</p> <p>2 A. Yes.</p> <p>3 Q. That's about exactly the same,</p> <p>4 correct?</p> <p>5 A. Yes. Yes.</p> <p>6 Q. But as it relates to folks who</p> <p>7 unfortunately were diagnosed with ovarian</p> <p>8 cancer, those who were asked that question</p> <p>9 before 2014, 36.5 percent of them reported</p> <p>10 talc use, right?</p> <p>11 A. (Nods head.)</p> <p>12 Q. And then that number shot up to</p> <p>13 51.5 percent after 2014, right?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. I see that.</p> <p>17 BY MS. BROWN:</p> <p>18 Q. And what the authors conclude</p> <p>19 on page 1416, is that although -- because</p> <p>20 of -- this is -- I'm reading from 1416, the</p> <p>21 first full sentence of the second column.</p> <p>22 "Because of publicity, we adjusted for date</p> <p>23 of interview. However, there is still a</p> <p>24 possibility that recall bias may have caused</p>	<p>1 correct?</p> <p>2 A. Yes.</p> <p>3 Q. And what method did you employ</p> <p>4 to assure yourself that those results were</p> <p>5 not confounded by recall bias?</p> <p>6 A. By reviewing the methods and</p> <p>7 analyzing the methods, just like we did with</p> <p>8 this paper.</p> <p>9 Q. And what did you find in the Wu</p> <p>10 article, for example, that leads you to</p> <p>11 believe that the findings were not the</p> <p>12 subject of recall bias?</p> <p>13 A. I would have to read the Wu</p> <p>14 materials and methods again. If you'd like</p> <p>15 me to, I will.</p> <p>16 Q. Well, did you undertake an</p> <p>17 analysis of the post-2014 papers with an</p> <p>18 effort to investigate whether the findings</p> <p>19 were subject to recall bias? That's my</p> <p>20 question.</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form. She's answered your question.</p> <p>23 A. When I reviewed all of the</p> <p>24 papers, that was one of the things -- bias is</p>
Page 311	Page 313
<p>1 some inflation of the OR" -- or the odds</p> <p>2 ratios, correct?</p> <p>3 A. But if you read the rest of</p> <p>4 that study, "Our data do not support that</p> <p>5 recall bias alone before or after 2014 would</p> <p>6 account for the associations with body powder</p> <p>7 and epithelial ovarian cancer. It was not</p> <p>8 statistically significantly different."</p> <p>9 Q. Did you consider the author's</p> <p>10 finding as it related to recall bias in</p> <p>11 evaluating the Schildkraut paper?</p> <p>12 A. I did.</p> <p>13 Q. And would you agree that</p> <p>14 particularly given the media attention to</p> <p>15 lawsuits beginning in 2014, that recall bias</p> <p>16 is a concern of the case-control studies?</p> <p>17 A. If there was a statistically</p> <p>18 significant change and difference in change</p> <p>19 in reporting, it might -- it might be</p> <p>20 something to consider, but there was not.</p> <p>21 Q. All of the studies that you</p> <p>22 identified -- or the three studies you</p> <p>23 identified as being "high quality," were all</p> <p>24 published after the lawsuits began in 2014,</p>	<p>1 one of the things you wanted to -- I wanted</p> <p>2 to look at and I looked at. And if you're</p> <p>3 asking me specifically about this one, you</p> <p>4 know, I can read through it and tell you what</p> <p>5 it was specifically.</p> <p>6 BY MS. BROWN:</p> <p>7 Q. No, I don't need specifics of</p> <p>8 the study. I was asking for your</p> <p>9 methodology. How do you -- how -- when you</p> <p>10 evaluate a paper post-2014, how do you --</p> <p>11 what methodology do you employ to make sure</p> <p>12 that the results are not inflated by the</p> <p>13 lawsuit media attention?</p> <p>14 MS. O'DELL: Objection to form,</p> <p>15 asked and answered.</p> <p>16 A. In all of the studies, I review</p> <p>17 the methodology, I look for any evidence of</p> <p>18 bias, recall bias or anything else. Not</p> <p>19 every study compared before 2014 and after</p> <p>20 2014. This one did. They found no</p> <p>21 significant difference in recall of use.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. They concluded that an</p> <p>24 inflation of the odds ratio due to recall</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 314</p> <p>1 bias could not be ruled out. Did you 2 consider that? 3 A. When you -- when I look at 4 their methods -- that was their -- that was 5 their interpretation of the data as a 6 possible explanation. When I look at the 7 results, the results showed that there was no 8 statistically significant difference between 9 before and after 2014. 10 Q. And so as it relates to their 11 conclusion, do you discount that? 12 MS. O'DELL: Object to the 13 form. 14 A. When I read conclusions of this 15 paper or any paper, these are -- these are 16 possible explanations. It's not facts. The 17 facts are the results. 18 BY MS. BROWN: 19 Q. And did you discount the 20 statistically significant effect modification 21 by interview year and date? 22 A. No. 23 MS. O'DELL: Object to form. 24 A. That was statistically</p>	<p style="text-align: right;">Page 316</p> <p>1 in young adulthood; is that right? 2 MS. O'DELL: Object to the 3 form. 4 A. I assumed they started using 5 powder sometime after menarche. 6 BY MS. BROWN: 7 Q. Okay. And the average age of 8 menarche is 12; is that right? 9 A. I think it's ten in the US now. 10 I know. 11 Q. My gosh. Good thing I have 12 boys. You say in your report that the 13 latency period for ovarian cancer is at least 14 20 years, correct? 15 A. Yes. 16 Q. Okay. And you would agree with 17 me that most of the prospective studies 18 enrolled women in their sort of mid -- 19 middle-age women to postmenopause women, so 20 women in their 40s and 50s, correct? 21 A. Yes. 22 Q. And so if those women began 23 using powder, as IARC concludes, in young 24 adulthood, they would have been approximately</p>
<p style="text-align: right;">Page 315</p> <p>1 significant. 2 BY MS. BROWN: 3 Q. You considered that? 4 A. Yes. 5 MS. BROWN: Let's take a break. 6 THE VIDEOGRAPHER: Going off 7 the record. The time is 3:24 p.m. 8 (Recess taken from 3:24 p.m. to 9 3:40 p.m.) 10 THE VIDEOGRAPHER: Back on the 11 record. The time is 3:40 p.m. 12 BY MS. BROWN: 13 Q. Dr. Wolf, in evaluating the 14 talc epidemiology, do you agree with IARC 15 that the use of talcum powder for feminine 16 hygiene is acquired in young adulthood? 17 Approximately 80 percent of the women who use 18 powder start before the age of 25? Do you 19 agree with that? 20 A. I'm going to agree with you on 21 adulthood. 22 Q. And so in evaluating the 23 epidemiology here, you assumed that most 24 folks in these studies started using powder</p>	<p style="text-align: right;">Page 317</p> <p>1 anywhere from, you know, ten- to 20- to 2 30-year users at the time they enrolled in 3 the study, correct? 4 MS. O'DELL: Object to the 5 form. 6 A. I don't think we know that for 7 sure because they weren't asked when they 8 started or how long they used it. 9 BY MS. BROWN: 10 Q. Did you consider that WHI did 11 do a subgroup analysis on women who used 12 powder for more than 20 years? 13 A. Yes. 14 Q. And what was the finding of 15 that, Doctor? 16 A. There was not a statistically 17 significant increased risk in those women. 18 Q. How did -- how does your 19 understanding of when powder use generally 20 begins in women and the latency period for 21 ovarian cancer, how does that inform your 22 critique that the prospective studies are not 23 long enough to detect ovarian cancer? 24 MS. O'DELL: Object to the</p>

80 (Pages 314 to 317)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 318</p> <p>1 form.</p> <p>2 A. The only thing that prospective</p> <p>3 studies looked at was one point in time, so</p> <p>4 we don't know how long. You can't -- you</p> <p>5 can't make a determination of a study based</p> <p>6 on thinking that's how long they used it.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Well, if the prospective study</p> <p>9 asked a 55-year-old if she was a talcum</p> <p>10 powder user, you would agree with me, based</p> <p>11 on your understanding of when people began</p> <p>12 using talcum powder, that she likely started</p> <p>13 in young adulthood, right?</p> <p>14 MS. O'DELL: Objection to form.</p> <p>15 A. I think the question was often</p> <p>16 ever use, and so I don't know if she started</p> <p>17 in young adulthood and did it for 20 or 30</p> <p>18 years, or she started at middle age and did</p> <p>19 it later, or she lived in the North and</p> <p>20 didn't use it and then moved to the South and</p> <p>21 started using it because she was hotter,</p> <p>22 because sweating is often a reason that</p> <p>23 people -- women give for using powder, and</p> <p>24 men. I don't know that I can infer that from</p>	<p style="text-align: right;">Page 320</p> <p>1 the witness has it.</p> <p>2 MS. O'DELL: Do you have the</p> <p>3 right one?</p> <p>4 THE WITNESS: I don't have</p> <p>5 page 305.</p> <p>6 MS. O'DELL: She has 100 C, not</p> <p>7 2010.</p> <p>8 THE WITNESS: I have 100 C.</p> <p>9 BY MS. BROWN:</p> <p>10 Q. Didn't we mark this?</p> <p>11 A. It's hiding. Here it is. Here</p> <p>12 it is.</p> <p>13 MS. O'DELL: Yeah, sorry,</p> <p>14 excuse me.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. And so my question was, to</p> <p>17 orient you, Doctor, I'll direct you to</p> <p>18 Section B, third paragraph, the conclusion</p> <p>19 there, that, "The use of talcum powder for</p> <p>20 feminine hygiene is acquired in young</p> <p>21 adulthood, since 80 percent of women who use</p> <p>22 body powder start before the age of 25. IARC</p> <p>23 cites Harlow and Weiss from 1989."</p> <p>24 Do you agree with that?</p>
<p style="text-align: right;">Page 319</p> <p>1 the data in the study.</p> <p>2 BY MS. BROWN:</p> <p>3 Q. Well, IARC has stated that 80</p> <p>4 percent of women who use body powder start</p> <p>5 before the age of 25. Do you agree with</p> <p>6 that?</p> <p>7 MS. O'DELL: If you need to</p> <p>8 look at that study --</p> <p>9 A. Yeah, I need to look at the</p> <p>10 IARC paper.</p> <p>11 BY MS. BROWN:</p> <p>12 Q. We have marked that as</p> <p>13 Exhibit 13. And it's page 305.</p> <p>14 A. I don't see that one, because</p> <p>15 it's a thick one. It's not here.</p> <p>16 Q. Did we mark IARC --</p> <p>17 MS. O'DELL: Here we go.</p> <p>18 A. Here we go.</p> <p>19 MS. O'DELL: What page?</p> <p>20 MS. BROWN: 305.</p> <p>21 MS. O'DELL: Actually, this is</p> <p>22 the wrong one. I'm assuming you're</p> <p>23 looking at 2010?</p> <p>24 MS. BROWN: Yeah. She had --</p>	<p style="text-align: right;">Page 321</p> <p>1 A. Yes.</p> <p>2 Q. Okay. And you know that the</p> <p>3 Nurses Health Study enrolled women -- middle</p> <p>4 age women, correct?</p> <p>5 A. Postmenopausal women.</p> <p>6 Q. Ages 30 to 55 in 1976, and that</p> <p>7 would have been ages 36 to 61 in 1982, right?</p> <p>8 A. I thought we were talking about</p> <p>9 the Women's Health Initiative. We're talking</p> <p>10 about the Nurses Health Study?</p> <p>11 Q. Well, one question is Nurses</p> <p>12 Health. We'll go to Women's Health next.</p> <p>13 A. All right.</p> <p>14 Q. And so if most women, majority</p> <p>15 80 percent, start at age 25, many of the</p> <p>16 women enrolled in Nurses Health, for example,</p> <p>17 would have already been using talcum powder</p> <p>18 for decades prior to enrollment in that</p> <p>19 study, correct?</p> <p>20 A. I'm just adding up. So they</p> <p>21 would have been aged 36 to 61.</p> <p>22 Q. Correct.</p> <p>23 A. So some of them might have,</p> <p>24 yes.</p>

81 (Pages 318 to 321)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 322</p> <p>1 Q. Well, at least everyone who was</p> <p>2 enrolled would have been using it for at</p> <p>3 least ten years, right?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. We don't know that. We're</p> <p>7 inferring from another paper where it was</p> <p>8 reported that 80 percent of women use it</p> <p>9 before age 25, that women who were asked did</p> <p>10 they ever use it had been using it their</p> <p>11 whole -- since age 25.</p> <p>12 BY MS. BROWN:</p> <p>13 Q. And in evaluating the</p> <p>14 epidemiology, did you make that conclusion?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. I didn't make that inference</p> <p>18 because it wasn't clear in the paper, that</p> <p>19 that was something that was considered or</p> <p>20 asked about how long they used it.</p> <p>21 BY MS. BROWN:</p> <p>22 Q. When you evaluated the Nurses</p> <p>23 Health Study, did you believe that the women</p> <p>24 ages 36 to 61, who were asked about talcum</p>	<p style="text-align: right;">Page 324</p> <p>1 BY MS. BROWN:</p> <p>2 Q. In evaluating the Women's</p> <p>3 Health Initiative data, you did consider the</p> <p>4 data that they had on folks who reported</p> <p>5 using powder for more than 20 years, right?</p> <p>6 A. Yes.</p> <p>7 Q. And you know that that resulted</p> <p>8 in a nonstatistically significant finding,</p> <p>9 correct?</p> <p>10 A. That's correct.</p> <p>11 Q. And so your critique, as it</p> <p>12 relates to the fact that the cohorts were not</p> <p>13 long enough, does not relate to the Women's</p> <p>14 Health Initiative; is that right?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. My critique does relate to the</p> <p>18 Women's Health Initiative, because even if</p> <p>19 they were using it for 20 -- more than 20</p> <p>20 years -- let me step back and say this, so</p> <p>21 that it's clear in my mind.</p> <p>22 I don't know at what point in</p> <p>23 their use that 20 years till cancer occurs</p> <p>24 starts. I don't know if it's after one dose,</p>
<p style="text-align: right;">Page 323</p> <p>1 powder use in 1982, had just begun using</p> <p>2 talcum powder?</p> <p>3 A. I don't know have any</p> <p>4 information --</p> <p>5 MS. O'DELL: Object to form.</p> <p>6 A. -- to confirm or dispute that.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Did you consider the</p> <p>9 information from IARC, that most women who</p> <p>10 use talcum powder start at age 25?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. But in the Nurses Health Study,</p> <p>14 I don't have that information about when they</p> <p>15 started.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. My question was, did you</p> <p>18 consider the information from IARC, that most</p> <p>19 women who use talcum powder start at age 25?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. And my answer is the two are</p> <p>23 not -- I can't draw a conclusion from one to</p> <p>24 the other.</p>	<p style="text-align: right;">Page 325</p> <p>1 if it's after a year, if it's after five</p> <p>2 years, if it's after ten years. When does</p> <p>3 that zero point go to 20 years, and I don't</p> <p>4 think there's any way we can know that.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. Is what you're saying, Doctor,</p> <p>7 you don't know how much talcum powder</p> <p>8 exposure is needed to cause ovarian cancer?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. I'm saying that in an</p> <p>12 individual patient, it might take a different</p> <p>13 amount and different time for ovarian cancer</p> <p>14 to develop as a result of talcum powder use.</p> <p>15 And so even guessing when the women started</p> <p>16 doesn't give me enough information to know</p> <p>17 when that lag period started or if that lag</p> <p>18 period is 20 years or if it might be up to 40</p> <p>19 years, which is reported in some studies as</p> <p>20 how long it takes to develop cancer from a</p> <p>21 toxin.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. In your opinion as a</p> <p>24 gynecologic oncology, what's the latency</p>

82 (Pages 322 to 325)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 326</p> <p>1 period for ovarian cancer?</p> <p>2 A. I'm going to answer you the way</p> <p>3 I answer all of my patients. And I don't</p> <p>4 think we know for sure. The only data that</p> <p>5 we actually have that I'm aware of is the</p> <p>6 Hiroshima data, that 15 to 20 years after the</p> <p>7 atomic bomb was dropped, but when patients</p> <p>8 come to me and they say, "How long had I had</p> <p>9 this cancer? When did this cancer develop?"</p> <p>10 Well, we never sit and watch somebody from</p> <p>11 the time they have the first hint of cancer,</p> <p>12 to know how long it takes to develop, or</p> <p>13 somebody who has a precancerous lesion,</p> <p>14 although there isn't a good one for ovarian</p> <p>15 cancer, so we don't know the answer to that.</p> <p>16 Q. So in fact, Doctor, the latency</p> <p>17 period for ovarian cancer could be even</p> <p>18 shorter than 15 or 20 years?</p> <p>19 MS. O'DELL: Objection to form.</p> <p>20 A. I don't know the latency period</p> <p>21 for sure. The only data that I -- you know,</p> <p>22 that is clear is the data after the bombs,</p> <p>23 and I think, could it be shorter, could it be</p> <p>24 longer...</p>	<p style="text-align: right;">Page 328</p> <p>1 dose versus somebody else.</p> <p>2 For instance, the</p> <p>3 African-Americans who have, genetically, a</p> <p>4 low -- it appears a low risk of ovarian</p> <p>5 cancer, there are individual differences in</p> <p>6 patients' intrinsic risk as well as any</p> <p>7 external risks.</p> <p>8 BY MS. BROWN:</p> <p>9 Q. Were you aware of any</p> <p>10 scientific article that has attempted to</p> <p>11 quantify the latency period between first</p> <p>12 exposure to perineal use of talc and the</p> <p>13 development of ovarian cancer?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. As far as my understanding, we</p> <p>17 don't have that information. And I think</p> <p>18 from my interpretation of reading the papers,</p> <p>19 it might be hard to confirm or deny that.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. Would you agree that one of the</p> <p>22 limitations of the talc epidemiology is the</p> <p>23 self-reported nature of talcum powder use and</p> <p>24 exposure?</p>
<p style="text-align: right;">Page 327</p> <p>1 BY MS. BROWN:</p> <p>2 Q. We don't know. Fair?</p> <p>3 MS. O'DELL: Objection to form.</p> <p>4 A. I think it's variable.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. Have you evaluated the</p> <p>7 case-control data and come to an opinion on</p> <p>8 the amount of time between exposure and</p> <p>9 development of ovarian cancer based on the</p> <p>10 case-control data?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. So I'm going to answer the same</p> <p>14 way, in that, I'm not sure that I can, based</p> <p>15 on an individual person's response to the</p> <p>16 powder and -- the talcum powder product and</p> <p>17 dosage, to be able to say what the latency</p> <p>18 period is.</p> <p>19 If I have someone who has some</p> <p>20 other intrinsic sensitivity risk for</p> <p>21 developing ovarian cancer or risk for</p> <p>22 developing ovarian cancer if they're exposed</p> <p>23 to talcum powder product, it might not take</p> <p>24 as long; it might not take the same amount of</p>	<p style="text-align: right;">Page 329</p> <p>1 MS. O'DELL: Objection to form.</p> <p>2 A. Anytime there's self-reporting</p> <p>3 of anything, it's one thing to consider as a</p> <p>4 potential bias in the study.</p> <p>5 BY MS. BROWN:</p> <p>6 Q. In your review of the talc</p> <p>7 epidemiology, did you find evidence of a dose</p> <p>8 response?</p> <p>9 A. Some of the papers do show</p> <p>10 evidence of a dose response and some do not.</p> <p>11 Q. Do you agree with the FDA in</p> <p>12 its 2014 denial of the citizen's petition</p> <p>13 that dose response evidence is lacking?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. I would say that if we look at</p> <p>17 the -- many of the studies published after</p> <p>18 2014, there does appear to be a dose</p> <p>19 response, and so that information wouldn't</p> <p>20 have been available. The Wu -- the original</p> <p>21 Wu study did show a response. The Cramer</p> <p>22 study 2016, the Schildkraut study, the</p> <p>23 Penninkilampi meta-analysis all showed some</p> <p>24 hint of a dose response. They wouldn't have</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 330</p> <p>1 had any of those, except the Wu. 2 BY MS. BROWN: 3 Q. And those studies did not -- 4 for example, Cramer did not show a dose 5 response with duration of use, right? 6 A. I thought they showed an 7 increase with frequency and duration of use. 8 Q. And so if you look, for 9 example, at Table 1 of Cramer, we actually 10 see a decrease in the risk after 35 years, 11 right? 12 A. Can I -- 13 Q. Absolutely. 14 A. Is that one of the exhibits? 15 Because it's not in there. 16 Q. Right. 17 A. Or I can't find it. 18 Q. We marked it as 11. 19 A. Yeah. 20 MS. O'DELL: Here we go. 21 A. Years used. So I'm looking at 22 Table 1. Is that what you're looking at? 23 BY MS. BROWN: 24 Q. Right. If you look at the</p>	<p style="text-align: right;">Page 332</p> <p>1 frequency, if you look at Table 1 continued 2 on the very next page, there was -- while 3 there was an increase of use up to 7200 4 applications, after 7200 applications, the 5 use decreased, right? 6 MS. O'DELL: Object to the 7 form. 8 A. No, the top part of that, it 9 goes up, it goes down, it goes back up. The 10 bottom part of that -- the last part of that 11 table is assuming 12 months per year 12 missing -- these are people with missing 13 months. 14 BY MS. BROWN: 15 Q. And so you agree there's not a 16 linear increase in frequency of application, 17 correct? 18 A. In this paper, there's not a 19 linear increase, but there is an increase 20 with more frequent application. And I want 21 to say, again, and I think I've said this 22 earlier, is that what's a dose? Frequency of 23 use, in my head, I can't get my head around, 24 is it the same amount every time? There</p>
<p style="text-align: right;">Page 331</p> <p>1 years used, you'd agree with me that there's 2 actually a slight decreased risk after 35 3 years of use? 4 A. But there's an increased risk 5 between 8 and 20, up to 35, and all of those 6 are fairly similar. 7 Q. And what Cramer himself 8 includes -- concludes, is that the trend for 9 years used was flat, right? 10 A. Yes. 11 Q. So what he did not find was 12 that the longer you used talcum powder, a 13 significant increase in your risk of ovarian 14 cancer, correct? 15 MS. O'DELL: Object to the 16 form. 17 A. The more frequently you used 18 it, an increase. 19 BY MS. BROWN: 20 Q. Right. But as to the number of 21 years, he did not find any dose response, 22 correct? 23 A. That's correct. 24 Q. And even to be fair as to the</p>	<p style="text-align: right;">Page 333</p> <p>1 isn't -- it's not like it's a 5-milligram 2 pill. It's powder in your panties. And to 3 look at any of this data and try to 4 equivocate dose, I think it's challenging. 5 Q. One of the things you say in 6 your report is, given those challenges, the 7 evaluation of a dose response was not as 8 important to your analysis; is that right? 9 A. Yes. 10 MS. O'DELL: Object to form. 11 BY MS. BROWN: 12 Q. And what -- and that's 13 different than the Bradford Hill criteria, 14 right? 15 MS. O'DELL: Object to the 16 form. 17 A. That's one of the tenets of the 18 Bradford Hill. It's not the only one. 19 BY MS. BROWN: 20 Q. Right. But in your analysis, 21 you determined that that factor of the 22 Bradford Hill was less important, correct? 23 A. Because it's hard to 24 quantitate, as I just stated, what's a dose.</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 334</p> <p>1 Even if you know for sure how many times 2 someone used talcum powder, you don't know 3 what dose they used and where it went. Did 4 it go all in their panties? Did it go on the 5 floor? Did it got in their groins? Did go 6 it up their backside? How much did they use? 7 None of these papers attempted 8 to and understandably it's hard to quantitate 9 how much is a dose. And so given that it's 10 challenging to answer the question about dose 11 response, it's hard to put a lot of weight on 12 that. 13 Q. And what you say in your report 14 at page 15, is that given the limitations of 15 the data, and those would be the limitations 16 you just described, right? 17 A. Yes. 18 MS. O'DELL: Objection to form. 19 BY MS. BROWN: 20 Q. And what that means is that 21 this product, the use of this product is 22 difficult to quantify, correct? 23 MS. O'DELL: Object to the 24 form.</p>	<p style="text-align: right;">Page 336</p> <p>1 their -- all of those things are hard to 2 quantify. 3 BY MS. BROWN: 4 Q. Is there any scientific data 5 that you are aware of that shows a particular 6 percentage of perineal powder reaching the 7 ovary? 8 A. I'm not aware that there's any 9 data that's ever looked at that. 10 Q. For purposes of your opinion, 11 however, you have assumed that some amount of 12 the powder that's applied perineally reaches 13 the ovary; is that right? 14 MS. O'DELL: Object to the 15 form. 16 A. I assume that there's migration 17 of talc particles through the open genital 18 tract to get to the ovary. 19 BY MS. BROWN: 20 Q. And for your opinion to hold 21 true, that talcum powder that reaches the 22 ovary causes ovarian cancer, is there a 23 particular amount of talcum powder in your 24 mind that needs to reach the ovary?</p>
<p style="text-align: right;">Page 335</p> <p>1 A. The dose of using this product 2 is difficult to quantify. 3 BY MS. BROWN: 4 Q. Right. And when you say "the 5 dose is difficult to quantify," that just -- 6 you're referring to just the dose that 7 somebody puts on their perineum or on their 8 underwear, right? 9 MS. O'DELL: Object to form. 10 A. Their exposure dose, I'm 11 referring to now -- wherever they put it on 12 their perineum. 13 BY MS. BROWN: 14 Q. So are you -- would you agree 15 that both the amount that they used is 16 difficult to quantify? Fair? 17 A. Yes. 18 Q. As well as the amount that 19 actually reaches the ovary, right? 20 MS. O'DELL: Object to the 21 form. 22 A. The amount they used, the 23 amount that reaches the ovary, their own body 24 sensitivity to whatever amount reaches</p>	<p style="text-align: right;">Page 337</p> <p>1 MS. O'DELL: Objection to form. 2 A. I think -- I have no idea what 3 that amount would be and I don't know that 4 that amount is the same for everyone. 5 BY MS. BROWN: 6 Q. Is there any scientific 7 literature on which you rely that establishes 8 that individuals are susceptible to talcum 9 powder in a different way? 10 A. Individuals are susceptible to 11 all cancer risk factors in a different way. 12 Everyone who has a BRC1 mutation doesn't get 13 ovarian cancer. Everyone who has a lynch 14 syndrome mutation doesn't get colon cancer. 15 There are individual differences in risk 16 factors. And everyone who uses 17 postmenopausal hormones doesn't get ovarian 18 cancer or breast cancer. So there are 19 individual differences. Everybody's made up 20 differently, has a different immune response. 21 So it only makes sense to me that if it's 22 different in every other circumstance, it's 23 going to be different in talcum powder use 24 exposure.</p>

85 (Pages 334 to 337)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 338</p> <p>1 Q. Based on your review of the 2 epidemiology, is it your opinion that 3 individuals are put at risk for ovarian 4 cancer through perineal exposure more likely 5 than through inhalation of genital talcum 6 powder? 7 MS. O'DELL: Object to the 8 form. 9 A. In my review of the 10 epidemiology, all of the studies are 11 particularly looking at perineal exposure. 12 So through -- through that lens, I believe 13 that most of the information in those studies 14 is looking at that particular question, 15 perineal exposure, not necessarily 16 inhalation. 17 BY MS. BROWN: 18 Q. When you're evaluating a 19 patient for a suspected ovarian cancer, do 20 you inquire about any markers of asbestos 21 exposure, like pleural plaques or 22 mesothelioma or anything like that, 23 interstitial fibrosis? 24 A. Do I inquire about them? Do</p>	<p style="text-align: right;">Page 340</p> <p>1 or may not be related to the patient's 2 cancer. 3 Q. Have you -- in connection with 4 that opinion, Dr. Wolf, have you evaluated 5 the epidemiology on the miners and millers of 6 cosmetic talcum powder? 7 A. I believe that's in the IARC 8 paper or study. 9 Q. You recall that IARC points to 10 that as some of the best evidence, that 11 inhalation of nonasbestiform talc is not 12 carcinogenic? 13 MS. O'DELL: Object to the 14 form. 15 A. I don't recall that specific 16 conclusion. I'd have to look at it again. 17 So are we talking about IARC 10? Which one 18 are you -- 19 BY MS. BROWN: 20 Q. I'm just asking if you recall 21 and if you considered that conclusion? 22 MS. O'DELL: Could you repeat 23 the question, please? 24</p>
<p style="text-align: right;">Page 339</p> <p>1 you mean do I investigate -- 2 Q. Yes. 3 A. -- if they have any of those, 4 yes. 5 Q. Do you believe that if talcum 6 powder was contaminated with asbestos, that 7 it would be causing asbestos-related 8 diseases, like mesothelioma? 9 MS. O'DELL: Object to the 10 form. 11 A. Do I believe that if talcum 12 powder is contaminated with asbestos, would 13 it cause mesothelioma? 14 BY MS. BROWN: 15 Q. Uh-huh. 16 A. That's your question? I do 17 believe that talcum powder is contaminated 18 with asbestos and I believe that it causes -- 19 it can increase the risk of both mesothelioma 20 of the ovary and epithelial ovarian cancer. 21 And I'm investigating for any signs of 22 abnormality in the chest, I'm looking for any 23 abnormalities, evidence of mesothelioma or 24 any other abnormalities in the chest that may</p>	<p style="text-align: right;">Page 341</p> <p>1 BY MS. BROWN: 2 Q. Do you recall and did you 3 consider IARC's conclusion, that some of the 4 best epidemiology as it relates to inhalation 5 of a nonasbestiform talc, is the miners and 6 the millers of cosmetic talc? 7 A. I do recall that. 8 Q. Does that make sense to you as 9 a gynecologic oncologist, that one of the 10 best places to look in the epi world would be 11 the folks who are exposed to inhalation the 12 most? 13 MS. O'DELL: Object to the 14 form. 15 A. It makes sense to look at a 16 group of people who are going to be exposed. 17 BY MS. BROWN: 18 Q. And in concluding, as you have 19 done here today, Doctor, that cosmetic talcum 20 powder is contaminated with asbestos, how, if 21 at all, did you consider the results of the 22 miners and miller studies that IARC points to 23 as some of the best evidence? 24 MS. O'DELL: Object to the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 342</p> <p>1 form, asked and answered.</p> <p>2 A. So I'm not sure what you're</p> <p>3 asking. What I believe I'm hearing is,</p> <p>4 you're asking if there's asbestos in talcum</p> <p>5 powder, why don't miners and millers get</p> <p>6 ovarian cancer?</p> <p>7 BY MS. BROWN:</p> <p>8 Q. Exactly. Have you considered</p> <p>9 the fact that that epidemiology shows no</p> <p>10 mesothelioma?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. That's a different question,</p> <p>14 because I'm not talking about mesothelioma.</p> <p>15 I'm talking about epithelial ovarian cancer.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. And a second ago I asked you if</p> <p>18 you thought that talc was contaminated with</p> <p>19 asbestos and people were really breathing it</p> <p>20 in, shouldn't it be causing mesothelioma in</p> <p>21 women? And I thought your testimony was yes.</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. No, you asked me do I</p>	<p style="text-align: right;">Page 344</p> <p>1 there's a lot of abnormalities in the lung</p> <p>2 from breathing in talcum powder. And I'm</p> <p>3 losing myself because I'm not sure of the</p> <p>4 question again. Should -- can you -- let me</p> <p>5 tell you what I think you're asking me.</p> <p>6 BY MS. BROWN:</p> <p>7 Q. Why don't I just rephrase the</p> <p>8 question and try to do this bit by bit.</p> <p>9 A. Okay.</p> <p>10 Q. You would agree that</p> <p>11 mesothelioma is a disease that is often</p> <p>12 caused by asbestos exposure?</p> <p>13 A. Yes.</p> <p>14 Q. Some people refer to it as a</p> <p>15 signature asbestos-related disease, correct?</p> <p>16 MS. O'DELL: If you know.</p> <p>17 A. I don't know that term</p> <p>18 "signature." That's not something that --</p> <p>19 BY MS. BROWN:</p> <p>20 Q. And you have offered the</p> <p>21 opinion here today that talcum powder is</p> <p>22 contaminated with asbestos, right?</p> <p>23 A. Yes.</p> <p>24 Q. And you have offered the</p>
<p style="text-align: right;">Page 343</p> <p>1 investigate if women who I think might have</p> <p>2 ovarian cancer might have abnormalities in</p> <p>3 the chest, including abnormalities associated</p> <p>4 with mesothelioma, and I said, yes, I do,</p> <p>5 because women with ovarian cancer often have</p> <p>6 abnormalities in the chest. Usually if they</p> <p>7 do, it's from their ovarian cancer, but</p> <p>8 certainly I'm looking at any other potential</p> <p>9 cause.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Understood. Bad question on my</p> <p>12 part. We're missing each other. If -- you</p> <p>13 hold the opinion that talcum powder is</p> <p>14 contaminated with asbestos. And my question</p> <p>15 is, if that were true, shouldn't we be seeing</p> <p>16 mesothelioma in the miners and the millers of</p> <p>17 cosmetic talcum powder?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. I'm not sure how to answer</p> <p>21 that, because I think that talcum powder has</p> <p>22 multiple components that could cause cancer.</p> <p>23 Is it only the asbestos that could be --</p> <p>24 certainly, in people who work in mines,</p>	<p style="text-align: right;">Page 345</p> <p>1 opinion that perineal use of talcum powder</p> <p>2 could reach the ovaries via inhalation,</p> <p>3 correct?</p> <p>4 A. Yes.</p> <p>5 Q. And so my question to you is,</p> <p>6 if talcum powder is really contaminated with</p> <p>7 asbestos and if women who use it perineally</p> <p>8 really do inhale it, shouldn't they be</p> <p>9 getting asbestos-related diseases like</p> <p>10 mesothelioma?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 A. I'm going to say that they</p> <p>14 might.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. And in forming that opinion,</p> <p>17 have you considered the epidemiology on the</p> <p>18 miners and millers of cosmetic talcum powder?</p> <p>19 A. Yes. That we just talked</p> <p>20 about.</p> <p>21 Q. Okay. And those studies show</p> <p>22 that the folks with the highest, highest</p> <p>23 exposure to cosmetic talcum powder via</p> <p>24 inhalation, don't get mesothelioma, right?</p>

87 (Pages 342 to 345)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 346</p> <p>1 MS. O'DELL: Object to the 2 form. 3 THE WITNESS: Are you just 4 objecting? 5 MS. O'DELL: Yes. 6 THE WITNESS: I wasn't sure if 7 I was supposed to answer or not. 8 A. In that study, those patients 9 did not get mesothelioma. So again, the 10 question is, might talcum powder applied 11 perineally cause ovarian cancer by -- via an 12 inhalation route? Yes, I think that could 13 happen. Do I think those people should be 14 getting mesothelioma, because I have evidence 15 that that talcum powder is contaminated with 16 mesothelioma? I don't know. Maybe. 17 BY MS. BROWN: 18 Q. Did you look, in evaluating the 19 occupational studies that IARC relies on in 20 concluding that heavy occupational exposure 21 to asbestos causes ovarian cancer, did you 22 look at how the relative risks for ovarian 23 cancer in those studies compared to the 24 relative risks for mesothelioma?</p>	<p style="text-align: right;">Page 348</p> <p>1 BY MS. BROWN: 2 Q. Does your current institution, 3 the Community Health Practice, does it advise 4 women that perineal use of talcum powder 5 causes ovarian cancer? 6 A. So in my practice, it's me, a 7 physician's assistant and a nurse 8 practitioner and one other GYN oncologist. I 9 do, my physician's assistant does, my nurse 10 practitioner does. I don't know about my 11 partner. 12 Q. And we talked a little bit 13 earlier about when you started that practice. 14 Do you recall when you started telling 15 patients your belief that talcum powder use 16 causes ovarian cancer? 17 A. I started asking my patients 18 about their use and telling them to stop or 19 not use it once I started reviewing all of 20 the literature and formed my opinion. 21 Q. You made a motion, all the 22 literature that's in front of you, right? 23 A. Yes. 24 Q. So you --</p>
<p style="text-align: right;">Page 347</p> <p>1 A. Yes. 2 Q. And what was the conclusion 3 there, Doctor? 4 A. The relative risks of 5 mesothelioma is higher. 6 Q. By how much? 7 A. I can't remember. A lot. 8 Q. Okay. So do you recall seeing 9 relative risks for ovarian cancers in the 1.5 10 to 2.5 range? 11 A. Yeah. 12 Q. And for mesothelioma in the 40 13 range? 14 A. Yes. 15 Q. And so if someone is truly 16 exposed to heavy amounts of asbestos through 17 inhalation, they -- based on that data that 18 IARC considered, they're far more likely to 19 get mesothelioma than ovarian cancer, right? 20 MS. O'DELL: Object to the 21 form. 22 A. If people are exposed to heavy 23 doses of asbestos, they're more likely to get 24 mesothelioma than ovarian cancer, yes.</p>	<p style="text-align: right;">Page 349</p> <p>1 MS. O'DELL: Which is not just 2 in front of you, but we're talking 3 about what's on the side table as 4 well. 5 THE WITNESS: Yes. 6 MS. BROWN: Fair. 7 BY MS. BROWN: 8 Q. So to be clear, you started the 9 practice of asking patients if they used 10 talcum powder after you had undertaken review 11 of the literature in connection with your 12 expert work, correct? 13 MS. O'DELL: Object to the 14 form. 15 A. After I undertook review of the 16 literature. 17 BY MS. BROWN: 18 Q. And I understand that you 19 undertook a review of the literature in 20 connection with your expert work, right? 21 A. That's when I read all of the 22 literature -- began reading all of the 23 literature. I was aware of some of the data, 24 but when I began reviewing all of the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 350</p> <p>1 literature, yes.</p> <p>2 Q. Okay. And so prior to that</p> <p>3 time, it was not your practice to ask</p> <p>4 patients whether or not they used talcum</p> <p>5 powder, correct?</p> <p>6 A. Not as a routine. However, if</p> <p>7 I saw somebody who, when I examined them,</p> <p>8 obviously was using talcum powder, I</p> <p>9 recommended they not use it. They stop.</p> <p>10 Q. Do you agree, Doctor, that much</p> <p>11 about ovarian cancer is shrouded in mystery,</p> <p>12 from causes to early detection to effective</p> <p>13 treatments?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. I would not agree with that</p> <p>17 statement.</p> <p>18 BY MS. BROWN:</p> <p>19 Q. Let's mark this as Exhibit 20.</p> <p>20 (Deposition Exhibit 20 marked</p> <p>21 for identification.)</p> <p>22 BY MS. BROWN:</p> <p>23 Q. Handing you, Doctor, an article</p> <p>24 entitled "The Future of Ovarian Cancer</p>	<p style="text-align: right;">Page 352</p> <p>1 Right?</p> <p>2 A. Yes.</p> <p>3 Q. And as of November 2015, that</p> <p>4 was information that you signed off on,</p> <p>5 correct?</p> <p>6 A. Yes.</p> <p>7 Q. Okay. And so as of</p> <p>8 November 2015, you do not believe that one of</p> <p>9 the well-known causes of ovarian cancer is</p> <p>10 talcum powder use. True?</p> <p>11 A. I can't remember the time. I</p> <p>12 can tell you that this was used as part of</p> <p>13 patient information in relationship to the</p> <p>14 company that I was working, and the point of</p> <p>15 this was not to talk about risk factors. It</p> <p>16 was to talk about the importance of diagnosis</p> <p>17 and informing women, the general lay</p> <p>18 population, about getting to a gynecologic</p> <p>19 oncologist if they had a pelvic mass.</p> <p>20 Q. The information contained in</p> <p>21 Exhibit 20 was meant for patients who --</p> <p>22 A. For women.</p> <p>23 Q. For women.</p> <p>24 A. For women.</p>
<p style="text-align: right;">Page 351</p> <p>1 Diagnosis is Now - Through These 4</p> <p>2 strategies," by Judy Wolf, November 11th,</p> <p>3 2015. Is this an article that you wrote,</p> <p>4 Doctor? First of all, is that your picture</p> <p>5 next to Judy Wolf on the first page?</p> <p>6 A. It is.</p> <p>7 Q. Okay. And this article, dated</p> <p>8 November 11th, 2015, has your byline and</p> <p>9 picture, right?</p> <p>10 A. It does.</p> <p>11 Q. Okay. And do you recall,</p> <p>12 during the time period that you were in the</p> <p>13 private sector, authoring a number of</p> <p>14 articles that were posted on a website called</p> <p>15 nopelvicmass.com?</p> <p>16 A. Yes.</p> <p>17 Q. And was this one of those</p> <p>18 articles potentially?</p> <p>19 A. Yes. Yes.</p> <p>20 Q. Okay. And as we just -- as I</p> <p>21 just read, the article that has your picture</p> <p>22 and name on it says, "So much about ovarian</p> <p>23 cancer is shrouded in mystery, from causes to</p> <p>24 early detection to effective treatments."</p>	<p style="text-align: right;">Page 353</p> <p>1 Q. Okay. And certainly as a</p> <p>2 doctor, as a gynecologic oncologist, you</p> <p>3 think it's important to be truthful with</p> <p>4 women when you write about issues concerning</p> <p>5 women's health, right?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. I don't see anything on here</p> <p>9 that was -- is untruthful.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. I'm not suggesting that. I was</p> <p>12 just asking you, that when you write, as you</p> <p>13 do often, information about women's health,</p> <p>14 you'd agree it's important to be truthful?</p> <p>15 A. Yes.</p> <p>16 Q. Because the intended recipient</p> <p>17 of your writing are women who have or may</p> <p>18 have ovarian cancer, right?</p> <p>19 A. Yes.</p> <p>20 (Deposition Exhibit 21 marked</p> <p>21 for identification.)</p> <p>22 BY MS. BROWN:</p> <p>23 Q. I'm handing you, Doctor, what</p> <p>24 we have marked as Exhibit 21 to your</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 354</p> <p>1 deposition. This is another article with 2 your name and picture, entitled "How to find 3 the best doctor for ovarian cancer." Do you 4 recall writing this article? 5 A. Not specifically, but I know I 6 did a lot of these while I was working at 7 Vermillion. 8 Q. Okay. And just to close the 9 loop, Exhibit 20, even though you don't 10 necessarily recall writing it, you don't 11 dispute this is something that you did write, 12 correct? 13 A. I'm not disputing that. 14 Q. Okay. And the same for 15 Exhibit 21, you don't dispute that this 16 article is something you wrote in December of 17 2015? 18 A. That's correct. 19 Q. Okay. And this, again, was an 20 article aimed at folks who -- women who may 21 be concerned about ovarian cancer, correct? 22 A. Yes. 23 Q. And one of the things you did 24 in this article was to identify risk factors</p>	<p style="text-align: right;">Page 356</p> <p>1 ovarian cancer, right? 2 A. Yes. 3 Q. And then the fourth is close 4 relatives with a history of breast cancer or 5 ovarian cancer at any age, right? 6 A. Yes. 7 Q. And then the fourth and fifth 8 have to do with the Ashkenazi Jewish 9 heritage, correct? 10 A. Yes. 11 Q. And one of the things you did 12 not list in December of 2015 as a risk factor 13 for ovarian cancer, was genital use of talcum 14 powder, correct? 15 A. I did not use -- list any 16 nonhereditary risk. 17 Q. And that would include talcum 18 powder, correct? 19 A. Including talcum powder, 20 endometriosis, obesity, any hormonal 21 replacement. 22 Q. Sorry. Are you done? 23 A. I'm done. 24 Q. And that's in part, Doctor,</p>
<p style="text-align: right;">Page 355</p> <p>1 for ovarian cancer. True? 2 A. All listed here are familial 3 risk factors. 4 Q. And the title of the section 5 you have in this -- well, first, you say, 6 "What are the odds," right? The odds of 7 getting ovarian cancer, right? And you say 8 one place to start is by considering your 9 risk factors. True? 10 A. Yes. 11 Q. All right. And then you state, 12 "You're more likely to be at risk of ovarian 13 cancer if" -- and then you have a number of 14 bullets, correct? 15 A. Yes. And all of those bullets 16 relate to genetic risk. 17 Q. Exactly. And so the first 18 deals with a first-degree relative, right? 19 A. Yes. 20 Q. The second is a prior history 21 of breast cancer, correct? 22 A. Yes. 23 Q. The third is a prior history of 24 breast cancer and a relative with breast or</p>	<p style="text-align: right;">Page 357</p> <p>1 because in December of 2015, you had not 2 formed the opinion that genital use of talcum 3 powder causes ovarian cancer. True? 4 MS. O'DELL: Object to the 5 form. 6 A. That was prior to my doing any 7 of the review of all the literature. 8 BY MS. BROWN: 9 Q. Right. And so at the time of 10 these articles, that Exhibit 20 and 21, you 11 did not hold the opinion that talcum powder 12 use perineally causes ovarian cancer, 13 correct? 14 A. I wasn't convinced, as I am 15 today. 16 Q. Have you done any prior expert 17 work, Dr. Wolf? 18 A. No. 19 Q. Have you reviewed any 20 individual plaintiff cases who are suing in 21 the talcum powder litigation? 22 A. No. 23 Q. Okay. Has the extent of your 24 involvement in the talcum powder litigation</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 358</p> <p>1 related to the report that we've been 2 discussing today? 3 A. Yes. 4 Q. Okay. And in total, does it 5 sound about right to you, you've charged the 6 plaintiffs' lawyers for about 83 hours in 7 connection with your work? 8 A. That seems about right. 9 Q. And your rate is \$600 an 10 hour -- 11 A. Yes. 12 Q. -- is that correct? And how 13 did you come up with that rate? 14 A. I asked -- I asked my friend 15 Ali, what do people usually charge for this 16 kind of thing, and then I kind of picked a 17 rate in -- what I felt like was in the 18 middle. 19 Q. And so if I wanted to know how 20 much money the plaintiffs' lawyers have paid 21 you in total for your work in the talc 22 litigation, I could multiply 600 by 83 and 23 that should be about right? 24 A. That should be about right.</p>	<p style="text-align: right;">Page 360</p> <p>1 report and the references and write a review 2 paper and submit it for publication. 3 Q. Have you done any work to that 4 end yet, Doctor? 5 A. I haven't. 6 Q. Do have you have any journals 7 in mind where you intend to submit that 8 review? 9 A. I haven't decided for sure yet. 10 The journals that I read the most and most 11 GYN oncologists read, are the GYN Oncology, 12 the Journal of Clinical Oncology, The Gray 13 Journal, the ACOG journal, which is called 14 The Green Journal. So I would probably 15 choose one of those because clinicians read 16 them. 17 Q. Are you a member of ACOG? 18 A. I am. 19 Q. And are you a member of SGO? 20 A. I am. 21 Q. And in forming your opinions in 22 this case, did you consider the risk factors 23 that ACOG and SGO recognize for ovarian 24 cancer?</p>
<p style="text-align: right;">Page 359</p> <p>1 Q. Do you have any additional 2 plans to do additional expert work for the 3 plaintiffs in the talc litigation? 4 A. I mean, completing out whatever 5 happens with this case. 6 Q. Other than what we're here 7 about today, right? 8 A. That's -- that's all I have 9 planned. 10 Q. Do you have a website in 11 connection with your current practice? 12 A. I do. 13 Q. And do you indicate on your 14 website that talcum powder causes ovarian 15 cancer? 16 A. I don't believe I talk about 17 any risk -- specific risk factors for ovarian 18 cancer. That website is to introduce 19 patients to who I am and how I like to 20 practice. 21 Q. Do you have any plans to 22 publicize your belief that talcum powder 23 causes ovarian cancer? 24 A. I actually do plan to take my</p>	<p style="text-align: right;">Page 361</p> <p>1 A. Yes. 2 Q. And are you aware that in their 3 patient-facing websites, as well as any of 4 their publicly related information about 5 ovarian cancer, neither SGO nor ACOG 6 identifies perineal use of talcum powder as a 7 risk factor for ovarian cancer? 8 A. I am aware of that. 9 Q. And do you believe that the 10 doctors and the scientists at SGO and ACOG 11 simply have not reviewed all of the data 12 regarding perineal use of talcum powder and 13 ovarian cancer? 14 A. It's my understanding that most 15 of the GYN oncologists probably have not 16 reviewed the literature to the extent of 17 which I have reviewed it. And given that the 18 volume of literature has increased recently, 19 it takes time for societies like SGO and ACOG 20 to come up with an opinion. It has to go 21 through a committee and various steps to come 22 out. I don't think this is something that's 23 risen to their attention enough. That's part 24 of the reason that I want to write a paper</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 362</p> <p>1 about it, to help inform my colleagues.</p> <p>2 Q. Have you contacted anyone at</p> <p>3 ACOG or SGO and told them that you think they</p> <p>4 need to update their website and list that</p> <p>5 talcum powder causes ovarian cancer?</p> <p>6 A. I haven't yet.</p> <p>7 Q. Do you intend to do that?</p> <p>8 A. I intend to write a letter to</p> <p>9 SGO with my concerns, asking them to review</p> <p>10 it. I think that's the first step, is they</p> <p>11 have to review the literature on their own.</p> <p>12 Q. And you have been doing this</p> <p>13 talcum powder work for the plaintiffs'</p> <p>14 lawyers for a little over a year now; is that</p> <p>15 right?</p> <p>16 A. Yes.</p> <p>17 Q. And during that time period,</p> <p>18 you haven't contacted any of your</p> <p>19 professional organizations to inform them of</p> <p>20 your view that talc causes ovarian cancer?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 A. I have talked to individual</p> <p>24 colleagues who practice GYN oncology, and I</p>	<p style="text-align: right;">Page 364</p> <p>1 BY MS. BROWN:</p> <p>2 Q. Okay. And it sounds like you</p> <p>3 nonetheless, have raised the issue with some</p> <p>4 folks at the coalition, correct?</p> <p>5 A. Yes.</p> <p>6 Q. And it sounds like they don't</p> <p>7 agree with your assessment, correct?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. The last time I raised it,</p> <p>11 which was in the spring, at the meeting that</p> <p>12 is in conjunction with the Society of GYN</p> <p>13 Oncology, they didn't want to address it,</p> <p>14 they didn't want to take it on as something</p> <p>15 to review.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. But do you think, generally,</p> <p>18 the doctors and the scientists at</p> <p>19 organizations like ACOG and SGO and the</p> <p>20 National Ovarian Cancer Coalition are working</p> <p>21 very hard to protect women's health issues?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. I think that all of those</p>
<p style="text-align: right;">Page 363</p> <p>1 have talked to the National Ovarian Cancer</p> <p>2 Coalition Medical Advisory Board, of which</p> <p>3 I'm on the board. I used to be on the</p> <p>4 advisory board. And at the time that I</p> <p>5 raised it, there wasn't a lot of interest in</p> <p>6 pursuing it.</p> <p>7 BY MS. BROWN:</p> <p>8 Q. And so one of the organizations</p> <p>9 you referenced and to your credit have done a</p> <p>10 lot of work with, is the National Ovarian</p> <p>11 Cancer Coalition, right?</p> <p>12 A. Yes.</p> <p>13 Q. And as you well know, as</p> <p>14 someone who's been very active in that</p> <p>15 organization, they too have a statement on</p> <p>16 talcum powder, right?</p> <p>17 A. Yes.</p> <p>18 Q. And the National Ovarian Cancer</p> <p>19 Coalition does not believe that the evidence</p> <p>20 supports that talcum powder causes ovarian</p> <p>21 cancer, right?</p> <p>22 MS. O'DELL: Object to form.</p> <p>23 A. That's what their statement</p> <p>24 says.</p>	<p style="text-align: right;">Page 365</p> <p>1 societies and many other advocacy groups are</p> <p>2 doing what they think is best to protect</p> <p>3 women's health.</p> <p>4 BY MS. BROWN:</p> <p>5 Q. Have you considered the</p> <p>6 possibility that these folks at ACOG, at SGO,</p> <p>7 at NCI, at FDA, at IARC have reviewed the</p> <p>8 same data that you have and come to a</p> <p>9 different conclusion?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. I don't have all of the</p> <p>13 information about what they've reviewed or</p> <p>14 not reviewed. And some of those, I know that</p> <p>15 they didn't have all of the data and some of</p> <p>16 them, like the National Ovarian Cancer</p> <p>17 Coalition, I know they haven't reviewed the</p> <p>18 data. I don't know that SGO has done that at</p> <p>19 any time recently. If you go to their</p> <p>20 website, they refer you to ACOG. So I can't</p> <p>21 make that statement.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. You don't have those -- sitting</p> <p>24 here as someone who's been active in the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 366</p> <p>1 women's health field for almost 30 years, you 2 don't have any reason to believe that the 3 folks at ACOG, SGO, FDA, NCI, CDC have not 4 kept up-to-date with the talc and ovarian 5 cancer epidemiology? 6 MS. O'DELL: Object to the 7 form, misstates her testimony, assumes 8 things not in the record. 9 A. My assumption is that some 10 people in all of those have probably read 11 some of the data. I'm not sure who, if 12 anyone, in any of those has looked at all of 13 the evidence in the way that I have done. 14 BY MS. BROWN: 15 Q. And the way that you've looked 16 at the evidence is by using sort of your 17 interpretation of Bradford Hill; is that 18 right? 19 MS. O'DELL: Object to the 20 form. 21 A. I would say evidence-based 22 medicine and then using the tenets of 23 Bradford Hill to explain how I interpreted 24 the data that I reviewed.</p>	<p style="text-align: right;">Page 368</p> <p>1 A. Because there's limitations in 2 the data that we'll never know the answer to. 3 Q. And as it relates to strength 4 of the association, in your review of the 5 data, what is the relative risk associated 6 with talcum powder use and ovarian cancer? 7 MS. O'DELL: Object to the 8 form. 9 A. The overall -- looking at the 10 studies as a whole, 1.3 to 1.4 odds ratio. 11 BY MS. BROWN: 12 Q. And do you consider that to be 13 a strong association? 14 A. I consider it to be a 15 consistent, reliable association. It doesn't 16 have to be a high number, and Bradford Hill 17 explains that in FedEx paper, that it's the 18 consistent association and finding that 19 association. It doesn't have -- it's not 20 number dependent. 21 Q. You'd agree that 1.3 and 1.4 is 22 not a high relative risk? 23 MS. O'DELL: Object to the 24 form.</p>
<p style="text-align: right;">Page 367</p> <p>1 BY MS. BROWN: 2 Q. I'm sorry to interrupt. And 3 your methodology, though, as it relates to 4 Bradford Hill, employs a methodology that has 5 less reliance on dose response, right? 6 MS. O'DELL: Object to the 7 form. 8 A. Not less reliance on dose 9 response, just that in this particular case, 10 determining what the dosage is makes it hard 11 to determine the dose response. 12 BY MS. BROWN: 13 Q. And you say in your report that 14 you consider that a less important factor, 15 right? 16 MS. O'DELL: Object to the 17 form. 18 BY MS. BROWN: 19 Q. And so that's your report on 20 page 15, I think we talked about this 21 earlier, "Given the limitations of the data, 22 I consider this to be a less important factor 23 compared to strength of association, 24 consistency and biologic mechanism"?</p>	<p style="text-align: right;">Page 369</p> <p>1 A. 1.3 and 1.4 is not 10, but 1.2 2 was the risk of hormone -- postmenopausal 3 hormone replacement therapy, and I believe 4 that's a real risk also. 5 BY MS. BROWN: 6 Q. Have you considered in your 7 review of the epi, the FDA's concern that the 8 studies that have found small positive 9 associations have lower confidence limits 10 that are pretty close to 1? Have you looked 11 into that? 12 MS. O'DELL: Object to the 13 form. 14 A. So when the odds ratio's 1.3, 15 your confident intervals might be close to 1 16 sometimes. However, if it doesn't cross 1, 17 it's statistically significant. 18 BY MS. BROWN: 19 Q. And one of the reasons -- do 20 you understand why the FDA is concerned if 21 the confidence interval is getting close to 22 1? 23 A. That it might be by random 24 chance, yes.</p>

Judith K. Wolf, M.D.

Page 370	Page 372
<p>1 Q. And do you share that concern</p> <p>2 as you evaluate the confidence intervals</p> <p>3 here?</p> <p>4 A. If I didn't see such a</p> <p>5 consistent average of 1.3 to 1.4, I would be</p> <p>6 more concerned about it. As a whole, I'm not</p> <p>7 concerned about it when I look at all of the</p> <p>8 evidence.</p> <p>9 Q. And when you say "consistent,"</p> <p>10 you're referring within the population</p> <p>11 case-control studies, right?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. Yes.</p> <p>15 BY MS. BROWN:</p> <p>16 Q. Because if you look at the</p> <p>17 prospective cohorts, there's not consistency</p> <p>18 in the case controls, right?</p> <p>19 A. When you look at the</p> <p>20 meta-analyses, everything as a whole, yes,</p> <p>21 1.3 to 1.4.</p> <p>22 Q. Okay. If you bear with me for</p> <p>23 just one minute, Dr. Wolf, I want to just</p> <p>24 make sure I'm not forgetting anything and</p>	<p>1 for me everything, other than talc, that you</p> <p>2 believe is in Johnson & Johnson baby powder</p> <p>3 and causes ovarian cancer.</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. What I believe is in talcum</p> <p>7 powder product and that can be -- cause</p> <p>8 inflammation and/or be carcinogenic is platy</p> <p>9 talc, fibrous talc, asbestos, heavy metals,</p> <p>10 including nickel, chromium and cobalt, and</p> <p>11 fragrance products that can be irritating and</p> <p>12 inflammatory.</p> <p>13 BY MS. BROWN:</p> <p>14 Q. And you have not formed an</p> <p>15 opinion in connection with your analysis, as</p> <p>16 to how much each of the items that you just</p> <p>17 listed make up baby powder, right?</p> <p>18 MS. O'DELL: Of a particular</p> <p>19 bottle, over time or --</p> <p>20 MS. BROWN: Any --</p> <p>21 MS. O'DELL: -- what's the</p> <p>22 context of the question?</p> <p>23 MS. BROWN: At all.</p> <p>24</p>
Page 371	Page 373
<p>1 then I'm going to turn the questioning over</p> <p>2 to some of my colleagues.</p> <p>3 When you say on page 8, "The</p> <p>4 risk elevation is 20-60 percent," do you</p> <p>5 think it's more like 30 to 40?</p> <p>6 A. I think if you look at all the</p> <p>7 papers, some of them are 20 and some of them</p> <p>8 are as high as 60.</p> <p>9 Q. And, of course, if the actual</p> <p>10 risk is as high as 60, Narod's critique is</p> <p>11 not accurate. Fair?</p> <p>12 A. That's the range of what's been</p> <p>13 reported. The average is 1.3 to 1.4, and I</p> <p>14 believe that's what he estimated the 200,000</p> <p>15 on.</p> <p>16 Q. Did you understand him to be</p> <p>17 estimating how many he needed to study if the</p> <p>18 true relative risk was 1.2?</p> <p>19 A. I don't remember if it was 1.2</p> <p>20 or 1.3.</p> <p>21 Q. Okay. Real quick, Doctor, I</p> <p>22 want to just make sure I understand your</p> <p>23 opinion as it relates to the composition of</p> <p>24 talcum powder. Do you believe that -- list</p>	<p>1 BY MS. BROWN:</p> <p>2 Q. I mean, have you attempted to</p> <p>3 quantify how much heavy metal is in baby</p> <p>4 powder?</p> <p>5 A. I haven't attempted to quantify</p> <p>6 it. The fact that there's any heavy metal in</p> <p>7 there that's carcinogenic is of concern.</p> <p>8 Q. And what are you relying on for</p> <p>9 your opinion that there's heavy metals in</p> <p>10 baby powder?</p> <p>11 A. So that I believe is in Julie</p> <p>12 Pier's -- let me find it -- deposition.</p> <p>13 Julie Pier -- Exhibit 47.</p> <p>14 Q. Other than Exhibit 47 to Julie</p> <p>15 Pier's deposition, are you relying on</p> <p>16 anything else to support your opinion that</p> <p>17 baby powder products are contaminated with</p> <p>18 heavy metals?</p> <p>19 A. And also the testing by Longo</p> <p>20 and Rigler.</p> <p>21 Q. Other than Julie Pier, Longo</p> <p>22 and Rigler, are you relying on anything else</p> <p>23 to support your opinion that heavy metals</p> <p>24 contaminate Johnson & Johnson baby powder</p>

Judith K. Wolf, M.D.

Page 374	Page 376
<p>1 products?</p> <p>2 A. No.</p> <p>3 Q. And as to asbestos, we reviewed</p> <p>4 your reliance materials before. You're</p> <p>5 relying on the articles you pointed me to,</p> <p>6 Hopkins Exhibit 28, Blount's testimony and</p> <p>7 her '91 article and Longo's reports, to</p> <p>8 support your opinion that talcum powder</p> <p>9 contains asbestos, correct?</p> <p>10 A. And also the deposition of</p> <p>11 Julie Pier.</p> <p>12 Q. And again, as it relates to</p> <p>13 asbestos, you haven't made a determination as</p> <p>14 to how much asbestos is contaminating talcum</p> <p>15 powder, right?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. I've made a determination that</p> <p>19 these testings show evidence of asbestos in a</p> <p>20 significant amount of talcum powder that was</p> <p>21 tested.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. Okay. But in terms of how much</p> <p>24 asbestos is in an individual bottle, you</p>	<p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I didn't say these cause</p> <p>4 ovarian cancer. I say that they're known to</p> <p>5 be carcinogenic and could be the cause of why</p> <p>6 talcum powder products causes ovarian cancer.</p> <p>7 And the other thing in there that I know can</p> <p>8 be inflammatory, from reading Dr. Crowley's</p> <p>9 report, are some of the fragrances that are</p> <p>10 used. And since inflammation is a risk</p> <p>11 factor and an initiator in -- leads -- is</p> <p>12 related to the progression of ovarian cancer,</p> <p>13 I have concerns about those.</p> <p>14 BY MS. BROWN:</p> <p>15 Q. And your opinion, then, Doctor,</p> <p>16 as I understand it, is that you're not sure</p> <p>17 which or what combination of all the items</p> <p>18 you just listed to me are working to cause</p> <p>19 cancer; is that right?</p> <p>20 MS. O'DELL: Object do the</p> <p>21 form.</p> <p>22 A. My opinion is that it's the</p> <p>23 talcum powder product as a whole that</p> <p>24 increases the risk of ovarian cancer, and</p>
Page 375	Page 377
<p>1 haven't attempted to quantify that, right?</p> <p>2 A. I haven't and it wouldn't</p> <p>3 change my opinion.</p> <p>4 Q. Okay. As it relates to fibrous</p> <p>5 talc, what are you relying on for your</p> <p>6 opinion that fibrous talc is contained in</p> <p>7 Johnson & Johnson baby powder products?</p> <p>8 A. I don't have it referenced</p> <p>9 here, but my understanding is that it's hard</p> <p>10 to get pure platy talc and it's always</p> <p>11 contaminated with some fibrous talc and I</p> <p>12 can't tell you where I've seen it, but I've</p> <p>13 seen it -- reports as small as 2 percent, as</p> <p>14 high as 20 percent.</p> <p>15 Q. And sitting here today, you're</p> <p>16 not sure of the site for that 2 to 20 percent</p> <p>17 fibrous talc?</p> <p>18 A. I'm not. No.</p> <p>19 Q. Other than platy talc, 2 to 20</p> <p>20 percent fibrous talc, some amount of heavy</p> <p>21 metals and some amount of asbestos, is there</p> <p>22 anything else you believe is in Johnson &</p> <p>23 Johnson baby powder products that causes</p> <p>24 ovarian cancer?</p>	<p>1 I've listed things that I know are in there</p> <p>2 that can be carcinogenic or inflammatory.</p> <p>3 BY MS. BROWN:</p> <p>4 Q. And to be clear, though, you</p> <p>5 don't have an opinion as to the amounts of</p> <p>6 any of the items you just listed for me as</p> <p>7 they appear in baby powder, right?</p> <p>8 MS. O'DELL: Object to the --</p> <p>9 object to the form.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. That was a bad question.</p> <p>12 Here's what I want to know. I understand</p> <p>13 your opinion is based on your assumption that</p> <p>14 fragrance, platy talc, fibrous talc, heavy</p> <p>15 metals and asbestos are in Johnson &</p> <p>16 Johnson's products, correct?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 A. It's in talcum powder product.</p> <p>20 BY MS. BROWN:</p> <p>21 Q. And that would include Johnson</p> <p>22 & Johnson's products, correct?</p> <p>23 A. Would include any talcum powder</p> <p>24 product.</p>

95 (Pages 374 to 377)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 378</p> <p>1 Q. Are you of the opinion that --</p> <p>2 we need to change the tape. Sorry.</p> <p>3 THE VIDEOGRAPHER: Going off</p> <p>4 the record. The time is 4:40 p.m.</p> <p>5 (Recess taken from 4:40 p.m. to</p> <p>6 4:52 p.m.)</p> <p>7 THE VIDEOGRAPHER: This marks</p> <p>8 the beginning of disk 4. Back on the</p> <p>9 record. The time is 4:52 p.m.</p> <p>10 BY MS. BROWN:</p> <p>11 Q. Dr. Wolf, before we took a</p> <p>12 break, we were discussing your opinion that</p> <p>13 J&J's talcum powder products contain</p> <p>14 fragrances, platy talc, fibrous talc, heavy</p> <p>15 metals and asbestos. Do you recall that?</p> <p>16 A. I do.</p> <p>17 Q. And my question for you,</p> <p>18 Doctor, is it your opinion that J&J's talcum</p> <p>19 powder products contained all of those things</p> <p>20 at all periods of time?</p> <p>21 A. Well, what I know for sure and</p> <p>22 what testing that I've seen shows, that</p> <p>23 evidence of asbestos, heavy metals from the</p> <p>24 '70s through the '90s and testing looking for</p>	<p style="text-align: right;">Page 380</p> <p>1 there's evidence of asbestos at least.</p> <p>2 Q. And that's the Longo testing</p> <p>3 you referred to earlier?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. Final question -- final</p> <p>6 area of questioning, Dr. Wolf, would be</p> <p>7 page 20 of your report. To be clear, you</p> <p>8 believe that the mechanism by which talcum</p> <p>9 powder causes cancer is chronic inflammation;</p> <p>10 is that right?</p> <p>11 A. This is a reference page. Are</p> <p>12 you looking at a different page?</p> <p>13 Q. Page 12 of your report?</p> <p>14 MS. O'DELL: You said 20.</p> <p>15 A. You said 20.</p> <p>16 BY MS. BROWN:</p> <p>17 Q. Sorry. Tired.</p> <p>18 A. I know. I understand. I</p> <p>19 believe it's inflammation that leads to</p> <p>20 oxidative stress that then causes DNA damage,</p> <p>21 and I believe with Saed's most recent papers,</p> <p>22 that it actually induces gene mutations that</p> <p>23 change ovarian epithelial cells and culture.</p> <p>24 Q. Do you rely on anyone else,</p>
<p style="text-align: right;">Page 379</p> <p>1 fibrous talc at that same time -- actually</p> <p>2 Longo tested for fibrous talc too and found</p> <p>3 it in 41 of 42 specimens. I don't know about</p> <p>4 the fragrance because I don't know how long</p> <p>5 this particular fragrance formulation has</p> <p>6 been used, if it's been -- how long it's been</p> <p>7 there. And platy talc and fibrous talc I</p> <p>8 would assume have always been there.</p> <p>9 Q. Have you done any investigation</p> <p>10 into the different source mines J&J has used</p> <p>11 over the years for its talcum powder</p> <p>12 products?</p> <p>13 A. They have used talcum powder</p> <p>14 from Vermont, from Italy -- I think Italy</p> <p>15 first and then Vermont and then China.</p> <p>16 Q. And do you believe that the</p> <p>17 components of talcum powder have changed over</p> <p>18 time?</p> <p>19 A. I believe that there's probably</p> <p>20 slight differences coming from different</p> <p>21 areas in the world. But as far as I can</p> <p>22 tell, the testing that I have seen throughout</p> <p>23 the Italian and Vermont and into early Asian,</p> <p>24 which I assume meant China, testing, that</p>	<p style="text-align: right;">Page 381</p> <p>1 other than Dr. Saed, for your opinion that</p> <p>2 talcum powder is -- do you believe that talc</p> <p>3 is genotoxic?</p> <p>4 A. I believe that Dr. Saed's paper</p> <p>5 that he found gene -- point gene mutations</p> <p>6 after application of talc -- talcum powder.</p> <p>7 Q. Do you believe that talcum</p> <p>8 powder is genotoxic to ovarian cells?</p> <p>9 A. I believe that his paper shows</p> <p>10 that there's genetic mutations that occur</p> <p>11 with exposure to talcum powder.</p> <p>12 Q. Independent of inflammation?</p> <p>13 A. Independent of inflammation.</p> <p>14 Q. So in fact, you think there are</p> <p>15 two ways by which talcum powder can cause</p> <p>16 ovarian cancer: Chronic inflammation and</p> <p>17 genetic mutations, correct?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. So chronic inflammation that</p> <p>21 leads to changes within the cell and changes</p> <p>22 the oxidative state that then causes,</p> <p>23 secondarily, cytokine stimulation and changes</p> <p>24 in the cell, and then Saed's paper also shows</p>

Judith K. Wolf, M.D.

Page 382	Page 384
<p>1 evidence of gene -- point gene mutations that 2 change the oxidative state of the cell to a 3 prone inflammatory state. 4 BY MS. BROWN: 5 Q. And other than Dr. Saed's work, 6 are you relying on any other published 7 literature to support your belief that talc 8 is genotoxic? 9 MS. O'DELL: Object to the 10 form. 11 A. Dr. Saed's work, as per my 12 review, is the most convincing data that I've 13 seen of genetic changes, separate from 14 inflammatory changes, when talc was exposed 15 to both ovarian epithelial cells, ovarian 16 cancer cell lines and fallopian tube 17 epithelial cell lines. 18 BY MS. BROWN: 19 Q. And one of the papers you cited 20 for us in your early footnotes, lists sort of 21 a weight of the hierarchy of evidence. Do 22 you recall that paper? 23 MS. O'DELL: Object to the 24 form.</p>	<p>1 BY MS. BROWN: 2 Q. And finally, Doctor, you 3 reference on page 12, in support of your 4 opinion -- page 12 of your report in support 5 of your opinion, that talcum powder causes 6 inflammation and oxidative stress in vitro 7 and in vivo. You reference the NTP study; is 8 that right? 9 A. Yes. 10 Q. Have you reviewed the FDA's 11 analysis of that NTP study? 12 A. I'm aware that they had some 13 concerns about the analysis. 14 Q. Do you share the concerns and 15 the -- first of all, you understand the FDA 16 concluded that the paper had serious flaws, 17 right? 18 MS. O'DELL: Object to the 19 form. 20 A. I understand that the FDA had 21 concerns about the paper. 22 BY MS. BROWN: 23 Q. Do you share those concerns? 24 A. I think that the NTP toxicology</p>
Page 383	Page 385
<p>1 BY MS. BROWN: 2 Q. You had a footnote 4 and 5, 3 some cites that dealt with sort of he weight 4 of the evidence, generally. Do you remember 5 those? 6 A. I just want to see what they 7 are, 4 and 5. 8 Q. Footnote 4 and 5. 9 A. These are talking about the 10 difference between cohort studies and 11 meta-analysis? 12 Q. Right. And they contained a 13 chart with a hierarchy of evidence. Do you 14 recall reviewing that? 15 A. Yes. 16 Q. And you would agree that expert 17 witness opinions are the very lowest rung of 18 that chart? 19 MS. O'DELL: Object to the 20 form. 21 A. I've referenced those charts in 22 relationship to evaluating cohort studies and 23 meta-analysis studies. 24</p>	<p>1 studies of talc is one of the pieces of 2 evidence that I believe supports that 3 inflammation occurs after talcum powder 4 application and can cause -- be a 5 carcinogenic -- mechanism of carcinogenesis. 6 Q. Do you agree with the 7 conclusion of the 1994 FDA workshop, that the 8 NTP study has no relevance to human risk? 9 MS. O'DELL: Object to the 10 form. 11 A. I believe that the NTP study 12 helps as an informative, along with all of 13 the other studies listed there, that talcum 14 powder causes inflammation and oxidative 15 stress in ovarian cells and in cells in 16 general and that this can be carcinogenic. 17 It's a piece of the evidence, not the whole 18 evidence. 19 BY MS. BROWN: 20 Q. Finally, Doctor, before I turn 21 the questioning over to my colleague, you 22 testified a little earlier that you plan to 23 write a review article based on the 24 information contained in your report?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 386</p> <p>1 A. Yes.</p> <p>2 Q. Do you have plans to disclose</p> <p>3 your work as an expert witness when you</p> <p>4 author that publication?</p> <p>5 A. Of course I would.</p> <p>6 Q. Would you plan to disclose the</p> <p>7 amount of money that you've made working for</p> <p>8 plaintiffs' lawyers in connection with that</p> <p>9 litigation -- paper?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. As I've never written a</p> <p>13 paper -- as I've never been an expert witness</p> <p>14 before, I don't know what you need to</p> <p>15 disclose as far as that. I know that if you</p> <p>16 have grant or funding for anything, you</p> <p>17 disclose the amount and who it's from. I'm</p> <p>18 assuming it would be the same for this, but I</p> <p>19 don't know. I would check with the journal</p> <p>20 and see what was required and do whatever was</p> <p>21 appropriate.</p> <p>22 BY MS. BROWN:</p> <p>23 Q. And finally, Doctor, do you</p> <p>24 know of any scientific support for the</p>	<p style="text-align: right;">Page 388</p> <p>1 think you can make the step to say that it's</p> <p>2 because their vagina was stretched out more.</p> <p>3 MS. BROWN: Thanks for your</p> <p>4 time today, Dr. Wolf. I'm going to</p> <p>5 hand it over to my colleague.</p> <p>6 Can we go off for a second?</p> <p>7 MR. KLATT: Yeah, let's do</p> <p>8 that.</p> <p>9 THE VIDEOGRAPHER: Going off</p> <p>10 the record. The time is 5:02 p.m.</p> <p>11 (Recess taken from 5:02 p.m. to</p> <p>12 5:06 p.m.)</p> <p>13 THE VIDEOGRAPHER: Back on the</p> <p>14 record. The time is 5:06 p.m.</p> <p>15 EXAMINATION</p> <p>16 BY MR. KLATT:</p> <p>17 Q. Good afternoon, Dr. Wolf.</p> <p>18 A. Good afternoon.</p> <p>19 Q. My name is Mike Klatt and I</p> <p>20 represent Imerys Talc America in this case.</p> <p>21 You said earlier that you were aware that</p> <p>22 Imerys is a mining company, correct?</p> <p>23 A. That's correct.</p> <p>24 Q. I'm going to skip around,</p>
<p style="text-align: right;">Page 387</p> <p>1 opinions that women who have had children</p> <p>2 have a stretched-out vaginal tract such that</p> <p>3 migration is more likely?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. I wouldn't put -- I would never</p> <p>7 say that women who have had children have a</p> <p>8 stretched-out vaginal tract. All women have</p> <p>9 an open vaginal tract. Women who have had</p> <p>10 multiple vaginal deliveries may or may not</p> <p>11 have a larger opening to their vagina than</p> <p>12 women who do not.</p> <p>13 BY MS. BROWN:</p> <p>14 Q. You haven't seen any data to</p> <p>15 suggest that having more kids increases your</p> <p>16 risk of ovarian cancer because more</p> <p>17 carcinogens can migrate to your ovaries,</p> <p>18 right?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. So that seems like a multistep</p> <p>22 question. I do believe that at least one of</p> <p>23 the case-control studies looked at parity as</p> <p>24 a possible risk factor. Personally, I don't</p>	<p style="text-align: right;">Page 389</p> <p>1 because I've just been following what's been</p> <p>2 going on today and I just have a lot of</p> <p>3 questions in different areas. So there's</p> <p>4 probably not going to be necessarily a</p> <p>5 logical progression. So if you'll just bear</p> <p>6 with me, I'd appreciate it.</p> <p>7 A. Okay.</p> <p>8 Q. A minute ago, I believe that</p> <p>9 Ms. Brown asked you, that if you end up</p> <p>10 writing a letter or a review article to any</p> <p>11 organization about talc and ovarian cancer,</p> <p>12 you think it's important to disclose that</p> <p>13 you've been an expert in litigation regarding</p> <p>14 talc and ovarian cancer, correct?</p> <p>15 A. Yes.</p> <p>16 Q. Do you think it's important</p> <p>17 that you specifically disclose that you've</p> <p>18 been a retained, paid witness for plaintiffs</p> <p>19 in talc ovarian cancer in making that</p> <p>20 disclosure?</p> <p>21 A. Again, I've never been an</p> <p>22 expert witness before. I don't know what the</p> <p>23 rules of what I have to disclose, so that</p> <p>24 anyone who reads my article can read it with</p>

Judith K. Wolf, M.D.

Page 390	Page 392
<p>1 all of the information. Whatever the journal 2 said I needed to disclose, I would disclose. 3 Q. But don't you think it's 4 important for your readers to know which side 5 you're involved in in this litigation? 6 MS. O'DELL: Object to the 7 form. 8 A. I don't know if that's 9 something that is routinely done. If it is, 10 I definitely would do that. 11 BY MR. KLATT: 12 Q. But I'm asking if you, 13 personally, think that's an important fact to 14 disclose. Wouldn't you want to know that if 15 you were a doctor not involved in this in 16 reading an article, which side the person who 17 authored the article was testifying for? 18 MS. O'DELL: Object to the 19 form. 20 BY MR. KLATT: 21 Q. Would that be important to you 22 to know? 23 A. I would want to know all the 24 information that I could know. I'm assuming</p>	<p>1 letter somewhere? 2 MS. O'DELL: Uh-huh. 3 A. And it has been accepted with 4 some reviewer comments, which Dr. Saed 5 addressed. I gave counsel one that was not 6 marked. 7 THE WITNESS: Is it on the 8 back? 9 A. Oh, yes, here. 10 BY MR. KLATT: 11 Q. And are there any peer review 12 or comments compared -- put forth in what 13 you're looking at? 14 A. The reviewer's -- yeah. Say 15 that question again. 16 Q. When people peer review an 17 article -- 18 A. Yes. 19 Q. -- they submit comments, 20 correct? 21 A. Yes. 22 Q. Suggestions for revising the 23 article or adding data or adding explanation 24 or whatever, correct?</p>
Page 391	Page 393
<p>1 that that's information that would be 2 required to be disclosed and I would disclose 3 it. 4 Q. Okay. Can you look at Exhibit 5 No. 4, which is Dr. Saed's manuscript. 6 A. Yes. 7 Q. That's not a published article, 8 correct? 9 A. It's an accepted article. 10 Q. Well, it hasn't even been peer 11 reviewed yet, correct? 12 A. No, it has been peer reviewed. 13 Q. Can you hand me the article? 14 Do you see how on multiple pages, virtually 15 every page in blueprint, it says "for peer 16 review"? 17 A. Yes. 18 Q. So that's being submitted for 19 peer review, correct? 20 MS. O'DELL: Object to the 21 form. 22 A. It has been submitted. It has 23 been reviewed. 24 THE WITNESS: Do we have the</p>	<p>1 A. Yes. 2 Q. Where are those comments 3 regarding Saed's article in what you're 4 looking at? 5 A. There's nothing here. There's 6 also a letter from Dr. Saed when he sent the 7 paper back in with the comments from the 8 reviewers and his addressing of those 9 comments. This article has the changes that 10 the reviewer has recommended. 11 Q. Have you seen this other 12 document that has the peer reviewer comments? 13 A. I have. 14 Q. I'm sorry? 15 A. I have seen his letter. I 16 don't recall that it has all the specific 17 comments. It has what he's viewing as him 18 addressing the comments, but I don't know if 19 there are comments or -- 20 Q. Do you have that letter with 21 you? 22 A. I thought I had it. 23 MS. O'DELL: No. I mean, I 24 think there may be some confusion on</p>

Judith K. Wolf, M.D.

Page 394	Page 396
<p>1 that point.</p> <p>2 BY MR. KLATT:</p> <p>3 Q. Well, if there's anything else</p> <p>4 regarding Dr. Saed that you've reviewed that</p> <p>5 you haven't brought here and marked as an</p> <p>6 exhibit, we'd request that, please.</p> <p>7 A. Okay.</p> <p>8 Q. Is that fine with you?</p> <p>9 A. Yes.</p> <p>10 Q. Now, looking at Dr. Saed's</p> <p>11 manuscript that's been marked as Exhibit 4,</p> <p>12 I'm going to turn you to --</p> <p>13 THE WITNESS: Do I have my own</p> <p>14 copy of that? Yes, here it is.</p> <p>15 BY MR. KLATT:</p> <p>16 Q. I'm going to turn you to</p> <p>17 page 12 of Exhibit 4.</p> <p>18 A. Yeah.</p> <p>19 Q. And do you see down at the</p> <p>20 bottom of the page, it says "Conflict of</p> <p>21 Interest"?</p> <p>22 A. Yes.</p> <p>23 Q. It says, "The corresponding</p> <p>24 author, Dr. Ghassam Saed, acted as a</p>	<p>1 listed here?</p> <p>2 A. Beasley Allen isn't listed here</p> <p>3 either.</p> <p>4 MS. O'DELL: Object to form.</p> <p>5 A. It just says he received a</p> <p>6 consulting fee. So I don't know where else</p> <p>7 the money -- what other money he used.</p> <p>8 BY MR. KLATT:</p> <p>9 Q. But Beasley Allen isn't even</p> <p>10 listed here, as you said, as a source of the</p> <p>11 money for his work, correct?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. That's correct.</p> <p>15 BY MR. KLATT:</p> <p>16 Q. Okay. This isn't an adequate</p> <p>17 conflict of interest disclosure, is it?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form. If you know. Don't guess.</p> <p>20 A. I'm assuming that this is the</p> <p>21 conflict of interest that they requested from</p> <p>22 Reproductive Scientists [sic], and if they</p> <p>23 accept it, then I consider it adequate.</p> <p>24</p>
Page 395	Page 397
<p>1 consultant regarding this topic for a fee,</p> <p>2 otherwise, the authors declared that there</p> <p>3 are no conflicts of interest."</p> <p>4 There's no disclosure there</p> <p>5 that Dr. Saed's involved in litigation on</p> <p>6 behalf of plaintiffs in talc ovarian cancer</p> <p>7 cases, is there?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. My assumption is that what</p> <p>11 Reproductive Scientists [sic] requested be</p> <p>12 disclosed is what is stated here. And so</p> <p>13 this is what it says.</p> <p>14 BY MR. KLATT:</p> <p>15 Q. Who paid the fee to Dr. Saed</p> <p>16 for doing this work?</p> <p>17 A. This particularly doesn't say.</p> <p>18 I'm assuming that attorneys paid the fee.</p> <p>19 Q. Do you know who paid?</p> <p>20 A. I believe that in support of</p> <p>21 some of this data -- of this research that he</p> <p>22 received money from Beasley Allen.</p> <p>23 Q. Okay. Other than Beasley</p> <p>24 Allen, what contributors to this work are</p>	<p>1 BY MR. KLATT:</p> <p>2 Q. So whatever the journal says is</p> <p>3 adequate is adequate in your mind?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 BY MR. KLATT:</p> <p>7 Q. Is that what you're saying?</p> <p>8 A. I'm saying that as far as --</p> <p>9 this is what's disclosed. The journal</p> <p>10 accepted the article. I'm assuming they</p> <p>11 considered it was adequate disclosure.</p> <p>12 Q. But if you're a physician, a</p> <p>13 gynecologic oncologist out there in the</p> <p>14 field, not involved in the talc ovarian</p> <p>15 cancer litigation and you ultimately read</p> <p>16 Dr. Saed's paper in Reproductive Scientists</p> <p>17 [sic], aren't you going to want to know that</p> <p>18 he was a paid witness for the plaintiffs in</p> <p>19 that litigation?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 BY MR. KLATT:</p> <p>23 Q. That's something you'd want to</p> <p>24 know, isn't it?</p>

100 (Pages 394 to 397)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 398</p> <p>1 MS. O'DELL: Object to the 2 form. 3 A. If I had questions about 4 exactly where the money came from, I would 5 call Dr. Saed and ask him. 6 BY MR. KLATT: 7 Q. Have you ever done that for any 8 article you've read in a journal? 9 A. I haven't. 10 Q. What do you know about the 11 Journal of Reproductive Sciences? 12 A. I don't know that much about 13 it. It's not a journal that I routinely 14 read. 15 Q. And as a gynecologic 16 oncologist, there's a certain set of journals 17 that you routinely review, correct? 18 A. Yes. 19 MS. O'DELL: Object to the 20 form. 21 BY MR. KLATT: 22 Q. And Reproductive Sciences is 23 not one of those, right? 24 A. It is not one of those.</p>	<p style="text-align: right;">Page 400</p> <p>1 A. In talcum-based body products, 2 my concerns for carcinogenesis are platy 3 talc, fibrous talc, asbestos, heavy metal, 4 specifically the ones that have been found, 5 nickel, chromium and cobalt and inflammation 6 from the fragrances, which I know that 7 inflammation is associated with ovarian 8 cancer and so I have concerns about all of 9 those. 10 Q. Well, having concerns is one 11 thing, but testifying based on a reasonable 12 degree of medical certainty that these things 13 are, in fact, a cause of ovarian cancer is a 14 different thing. So is it your opinion that 15 all of these items, platy talc, fibrous talc, 16 asbestos, nickel, chromium, cobalt and 17 fragrance are contributing causes of ovarian 18 cancer in women who use talc-based body 19 powder products? 20 MS. O'DELL: Object to the 21 form. 22 A. It's my opinion that 23 talcum-based -- perineum use of talcum-based 24 body products causes ovarian cancer in some</p>
<p style="text-align: right;">Page 399</p> <p>1 Q. Had you ever heard of it 2 before? 3 A. I can't tell you if I've ever 4 heard of it. I've heard of lots of journals 5 over the years and I don't remember all of 6 them. 7 Q. You don't remember of ever 8 hearing of Reproductive Sciences before you 9 saw Exhibit 4, correct? 10 A. I can't recall. 11 Q. Now, earlier, you said in 12 response to Ms. Brown's questions, that 13 things that you feel like may be playing a 14 role in talc-based body powder products and 15 ovarian cancer, if I got it right, were platy 16 talc; is that right? 17 MS. O'DELL: Object to the 18 form. If you're going to go -- I'll 19 object each time, but I object to the 20 preparatory language. 21 BY MR. KLATT: 22 Q. What things in talc-based body 23 powder products do you think cause ovarian 24 cancer?</p>	<p style="text-align: right;">Page 401</p> <p>1 women and increases the risk in all. When I 2 look to see what is in it that could be 3 dangerous, potentially dangerous to women, I 4 see some things that are known to be 5 carcinogenic, such as fibrous talc and 6 asbestos and heavy metals. I see some things 7 that are possibly carcinogenic, such as platy 8 talc, and I see fragrances that are known to 9 be irritating and causing inflammation. 10 BY MR. KLATT: 11 Q. Do you think any one of those 12 things by itself is capable of causing 13 ovarian cancer in women who use talc-based 14 body powder products? 15 A. I didn't evaluate the data that 16 way and I don't look at the product that way. 17 I'm looking at it as a whole. 18 Q. So if you testify in the 19 hearing of Judge Wolfson this year and she 20 asks you, because judges can ask witnesses 21 questions, which one of these items that 22 you've mentioned are capable by themselves of 23 causing ovarian cancer in women using 24 talc-based body powder products, you're going</p>

Judith K. Wolf, M.D.

Page 402	Page 404
<p>1 to tell her you can't tell her which one of 2 these is capable by itself? 3 MS. O'DELL: Object to the 4 form, misstates her testimony. 5 A. I'm going to tell her just what 6 I said, that I evaluated the product as a 7 whole and I found evidence of multiple 8 carcinogenic, possibly carcinogenic and 9 inflammatory substances that could account 10 for that. Because they're all in the 11 product, I can't separate them out and say 12 which one is causing it. 13 BY MR. KLATT: 14 Q. And you can just say that they 15 possibly cause it, correct, not that they 16 probably cause it? 17 MS. O'DELL: Object to the 18 form, misstates her testimony. 19 BY MR. KLATT: 20 Q. You just said "possibly." 21 Didn't I understand that? 22 MS. O'DELL: Object to the 23 form. That's not what she said. 24</p>	<p>1 understand. 2 A. So let me list them again. 3 Platy talc has been determined to be possibly 4 carcinogenic, asbestos has been determined to 5 be carcinogenic, fibrous talc has been 6 determined to be carcinogenic, nickel and 7 chromium are -- have been determined to be 8 carcinogenic, cobalt has been determined to 9 be possibly carcinogenic, and the 10 fragrances -- some of the substances in the 11 fragrance are known to be inflammatory or 12 cause -- inflammatory or irritating. 13 And therefore, when I look at 14 the product of the whole, with all of that 15 spectrum of stuff in it, things in it, that 16 at the very least some are, the fragrances 17 are inflammatory and/or irritating and at the 18 very most, several are known to be 19 carcinogenic, that it's the combination of 20 that that increases the risk of ovarian 21 cancer in women who use perineal talcum 22 powder product. 23 BY MR. KLATT: 24 Q. Are any of these things that</p>
Page 403	Page 405
<p>1 BY MR. KLATT: 2 Q. Let's read it back. I think 3 you just said "possibly cause," correct? 4 MS. O'DELL: Object to the 5 form. 6 A. No, that's not what I said. I 7 said there are multiple that are 8 carcinogenic, possibly carcinogenic and 9 inflammatory. 10 BY MR. KLATT: 11 Q. So you're saying they're 12 possibly carcinogenic -- 13 A. No, I'm saying some of the 14 agents -- 15 Q. Let me finish -- not probably 16 carcinogenic, correct? 17 MS. O'DELL: Excuse me. 18 A. No. 19 MS. O'DELL: Excuse me, let me 20 object. Object to the testimony -- 21 excuse me, object to the question 22 because it misrepresents her 23 testimony. 24 You may answer if you</p>	<p>1 you've listed by themselves capable of 2 causing ovarian cancer in women who use 3 talc-based body powder products? 4 A. I'm not aware that anybody has 5 looked at using any of those things by 6 themselves to cause -- to assess the risk of 7 ovarian cancer. And since the product 8 contains all of them, I don't know how that 9 can be evaluated. 10 Q. So if you evaluated the 11 talc-based body powder product as a whole 12 with all these things in them, you weren't 13 just evaluating Imerys raw talc by itself, 14 correct? 15 MS. O'DELL: Object to the 16 form. 17 A. I was evaluating the product. 18 BY MR. KLATT: 19 Q. The product as used by women? 20 A. The product as used by women -- 21 the product as used by women. 22 Q. Which is the product that sold 23 off the shelf, correct? 24 MS. O'DELL: Object to the</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 406</p> <p>1 form.</p> <p>2 A. The product that women could</p> <p>3 obtain to use on their perineum.</p> <p>4 BY MR. KLATT:</p> <p>5 Q. From retail stores, correct?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. From wherever they get it.</p> <p>9 BY MR. KLATT:</p> <p>10 Q. And you understand Imerys</p> <p>11 doesn't sell any talc directly to women?</p> <p>12 A. I understand that.</p> <p>13 Q. And you understand fragrance is</p> <p>14 added after the talc leaves Imerys'</p> <p>15 possession?</p> <p>16 A. I understand that.</p> <p>17 Q. Do any and all forms of</p> <p>18 inflammation cause or contribute to ovarian</p> <p>19 cancer?</p> <p>20 A. In the studies on inflammation</p> <p>21 in ovarian cancer, it's -- and most cancers</p> <p>22 and inflammation, it's the concern of chronic</p> <p>23 inflammation. T cells, lymphocytes, macro</p> <p>24 fascias causing changes in the oxidation</p>	<p style="text-align: right;">Page 408</p> <p>1 A. There's never been any evidence</p> <p>2 of that, that I'm aware of.</p> <p>3 Q. When you -- you've done</p> <p>4 abdominal surgeries on hundreds, if not maybe</p> <p>5 even thousands of women in your career,</p> <p>6 correct?</p> <p>7 A. Yes.</p> <p>8 Q. Now, that surgery itself can</p> <p>9 cause fibrosis, inflammation and adhesions,</p> <p>10 correct?</p> <p>11 A. That's correct.</p> <p>12 Q. And those adhesions can be</p> <p>13 long-term complications for women, correct?</p> <p>14 A. Yes.</p> <p>15 Q. And that's a form of</p> <p>16 inflammation, correct?</p> <p>17 A. It's a form of acute</p> <p>18 inflammation that leads to a scar or</p> <p>19 fibrosis.</p> <p>20 Q. And that's exactly what talc</p> <p>21 leads to, correct?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. There's not evidence of chronic</p>
<p style="text-align: right;">Page 407</p> <p>1 making free -- oxygen free radicals that can</p> <p>2 cause changes in the DNA. Not so much</p> <p>3 concerned about acute inflammation, but</p> <p>4 chronic inflammation.</p> <p>5 Q. Do all forms of chronic</p> <p>6 inflammation cause ovarian cancer?</p> <p>7 A. I'm not sure what forms of</p> <p>8 chronic inflammation you're asking about.</p> <p>9 Q. Well, are you saying that</p> <p>10 chronic inflammation inevitably can cause</p> <p>11 ovarian cancer?</p> <p>12 A. Chronic inflammation is a cause</p> <p>13 of ovarian cancer. You could have chronic</p> <p>14 inflammation and not get ovarian cancer.</p> <p>15 Q. Are you aware that corn</p> <p>16 starch-based body powder can cause</p> <p>17 granulomas, adhesions, fibrous tissue</p> <p>18 reactions and it's been banned by the FDA</p> <p>19 from surgical gloves and from patient</p> <p>20 examination gloves?</p> <p>21 A. I am aware of that.</p> <p>22 Q. Does the granulomas and</p> <p>23 adhesions and fibrosis that corn starch</p> <p>24 causes in patients cause ovarian cancer?</p>	<p style="text-align: right;">Page 409</p> <p>1 inflammation in adhesions secondary to</p> <p>2 surgery. There's an acute reaction and</p> <p>3 change and then fibrosis can occur, and</p> <p>4 that's what adhesions are, are fibrosis.</p> <p>5 BY MR. KLATT:</p> <p>6 Q. And that's what happens when</p> <p>7 talc in sufficient amounts is placed inside</p> <p>8 the body, the exact same thing, correct,</p> <p>9 Dr. Wolf?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. It's one of the things that can</p> <p>13 happen when talc is placed inside the body.</p> <p>14 BY MR. KLATT:</p> <p>15 Q. Well, is there anything else</p> <p>16 other than that type of tissue reaction that</p> <p>17 talc can cause?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. Yes. When talcum powder --</p> <p>21 when talc was placed, in an animal study, in</p> <p>22 the bursa of rat's ovaries, there was</p> <p>23 proliferation and precancerous changes in the</p> <p>24 ovaries.</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 410</p> <p>1 BY MR. KLATT:</p> <p>2 Q. Did those animals develop</p> <p>3 ovarian cancer?</p> <p>4 A. They did not. But they were</p> <p>5 sacrificed in a short period of time.</p> <p>6 Q. Can you name for me a single</p> <p>7 animal study that you've ever seen, where</p> <p>8 talc caused ovarian cancer in the animals?</p> <p>9 A. I cannot.</p> <p>10 Q. Can you name -- in fact, can</p> <p>11 you name for me any animal study you've ever</p> <p>12 seen, where asbestos put in animals caused</p> <p>13 ovarian cancer?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. So ovarian cancer is quite rare</p> <p>17 in most animals and so it's very difficult to</p> <p>18 have an animal model of something that causes</p> <p>19 ovarian cancer.</p> <p>20 BY MR. KLATT:</p> <p>21 Q. You know there's animal models</p> <p>22 of peritoneal mesothelioma due to asbestos,</p> <p>23 correct?</p> <p>24 A. I do.</p>	<p style="text-align: right;">Page 412</p> <p>1 ovarian cancer?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. Are you asking about my</p> <p>5 anecdotal experience?</p> <p>6 BY MR. KLATT:</p> <p>7 Q. No, I'm asking you for the</p> <p>8 medical evidence that you know, that these</p> <p>9 types of long-term adhesions resulting from</p> <p>10 surgery itself don't cause ovarian cancer in</p> <p>11 your patients?</p> <p>12 A. I'm not aware of any literature</p> <p>13 that suggests or supports that.</p> <p>14 Q. Has it ever been studied?</p> <p>15 A. I'm not aware of any studies</p> <p>16 that have been published about that.</p> <p>17 Q. Well, if it hasn't been</p> <p>18 studied, you can't say it doesn't cause</p> <p>19 ovarian cancer, can you?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 BY MR. KLATT:</p> <p>23 Q. You just don't know?</p> <p>24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 411</p> <p>1 Q. Are there animal models that</p> <p>2 show that asbestos instilled in animals'</p> <p>3 abdominal cavities can cause ovarian cancer?</p> <p>4 A. Not that I'm aware of.</p> <p>5 Q. Do you warn women before you do</p> <p>6 surgery on them, that your surgery can cause</p> <p>7 inflammation and adhesion -- long-term</p> <p>8 adhesion formation that could cause ovarian</p> <p>9 cancer?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. I inform my patients that</p> <p>13 surgery can cause inflammation and adhesions.</p> <p>14 BY MR. KLATT:</p> <p>15 Q. Can that cause ovarian cancer?</p> <p>16 A. Not the adhesions that are</p> <p>17 formed from the acute inflammation from</p> <p>18 surgery. I would also say that 90-plus</p> <p>19 percent of my patients, their ovaries come</p> <p>20 out when I operate on them.</p> <p>21 Q. How do you know that these</p> <p>22 long-term adhesions that result from</p> <p>23 abdominal surgery that you've done on</p> <p>24 hundreds of patients doesn't result in</p>	<p style="text-align: right;">Page 413</p> <p>1 form.</p> <p>2 A. I haven't seen any studies</p> <p>3 about it.</p> <p>4 BY MR. KLATT:</p> <p>5 Q. So if something is not studied,</p> <p>6 that means it doesn't occur?</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form.</p> <p>9 A. That's not what I said.</p> <p>10 BY MR. KLATT:</p> <p>11 Q. Right. Simply because there's</p> <p>12 no studies doesn't prove that adhesions after</p> <p>13 surgery don't cause ovarian cancer, correct?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 BY MR. KLATT:</p> <p>17 Q. You'd have to do studies to</p> <p>18 know that.</p> <p>19 MS. O'DELL: Excuse me. Object</p> <p>20 to the form.</p> <p>21 A. I don't believe those are</p> <p>22 studies that could be done.</p> <p>23 BY MR. KLATT:</p> <p>24 Q. So there are no such studies</p>

Judith K. Wolf, M.D.

Page 414	Page 416
<p>1 that you're aware of, correct?</p> <p>2 A. Not that I'm aware of.</p> <p>3 Q. You cited about 20 Imerys</p> <p>4 documents in -- as something that were</p> <p>5 materials that you considered.</p> <p>6 A. Yes.</p> <p>7 Q. Is that correct?</p> <p>8 A. Uh-huh.</p> <p>9 Q. Were you give a much larger set</p> <p>10 of Imerys documents and you picked those 20</p> <p>11 or were those 20 handpicked for you by the</p> <p>12 lawyers?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. Those documents were provided</p> <p>16 to me by the lawyers.</p> <p>17 BY MR. KLATT:</p> <p>18 Q. So you didn't look at a much</p> <p>19 larger set of Imerys documents yourself and</p> <p>20 select those 20 yourself, correct?</p> <p>21 A. The one that -- ones that are</p> <p>22 listed on my contributing data list are the</p> <p>23 ones that I saw.</p> <p>24 Q. The only ones you saw, correct?</p>	<p>1 who the company -- what the company it came</p> <p>2 from, and the mine, if it's -- if it's noted,</p> <p>3 and any comments.</p> <p>4 Q. But my point is, you don't know</p> <p>5 that any of these talc samples ended up in</p> <p>6 any body powder products, correct?</p> <p>7 A. I don't have that information</p> <p>8 on these.</p> <p>9 MS. O'DELL: Object to form.</p> <p>10 BY MR. KLATT:</p> <p>11 Q. I'm sorry?</p> <p>12 A. I don't have that information</p> <p>13 on these charts.</p> <p>14 Q. Are you aware the Imerys</p> <p>15 supplies talc to many industries that have</p> <p>16 nothing to do with body powder?</p> <p>17 A. I am aware of that.</p> <p>18 Q. Do you understand that there's</p> <p>19 types of talc that are caused -- called</p> <p>20 industrial talc that are not used for</p> <p>21 personal use or cosmetic products?</p> <p>22 A. Yes.</p> <p>23 Q. Do you have any idea which one</p> <p>24 of these on Exhibit 47 might fall into the</p>
Page 415	Page 417
<p>1 A. Yes.</p> <p>2 Q. And those were picked by the</p> <p>3 lawyers and not by you?</p> <p>4 MS. O'DELL: Object to form.</p> <p>5 A. Those were given to me by the</p> <p>6 lawyers.</p> <p>7 BY MR. KLATT:</p> <p>8 Q. You said earlier -- you</p> <p>9 referred to Julie Pier, an Imerys scientist,</p> <p>10 her Exhibit 47 in her MDL deposition. Do you</p> <p>11 recall that?</p> <p>12 A. Yes.</p> <p>13 Q. You can't point to me to a</p> <p>14 single talc sample that she tested in</p> <p>15 Exhibit 47 that you can show me ended up in</p> <p>16 talc-based body powders, can you?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 A. Can I look at it?</p> <p>20 BY MR. KLATT:</p> <p>21 Q. Sure.</p> <p>22 A. What I see on here is the date,</p> <p>23 what the material was, who did the testing,</p> <p>24 what the sample was, what the test revealed,</p>	<p>1 industrial talc category rather than the</p> <p>2 cosmetic talc category?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. It doesn't say on this list</p> <p>6 where the talc falls in.</p> <p>7 BY MR. KLATT:</p> <p>8 Q. And on many of these tests,</p> <p>9 there's not even any asbestos identified at</p> <p>10 all, correct?</p> <p>11 A. On some of them.</p> <p>12 Q. Are you aware that certain</p> <p>13 types of asbestos are ubiquitous in the</p> <p>14 environment?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. I am aware of that.</p> <p>18 BY MR. KLATT:</p> <p>19 Q. And you're aware that when talc</p> <p>20 is tested for asbestos, that there can be</p> <p>21 occasional asbestos particles on the test</p> <p>22 equipment itself, correct?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form. Don't guess. If you know --</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 418</p> <p>1 A. I don't -- I mean, I don't know</p> <p>2 that. I don't have evidence to support that.</p> <p>3 BY MR. KLATT:</p> <p>4 Q. Well, are you aware that in</p> <p>5 various test methodologies testing talc to</p> <p>6 see whether it has asbestos, that those</p> <p>7 methods take into account that there may be</p> <p>8 occasional contamination of the test</p> <p>9 equipment by asbestos that has nothing to do</p> <p>10 with the sample being tested?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 BY MR. KLATT:</p> <p>14 Q. Are you aware of that?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 Don't speculate, Dr. Wolf. If</p> <p>18 you know, please say so. If you</p> <p>19 don't --</p> <p>20 A. I don't know.</p> <p>21 BY MR. KLATT:</p> <p>22 Q. If you turn over on the back of</p> <p>23 page -- or second page of Exhibit 47 to</p> <p>24 Ms. Pier's deposition.</p>	<p style="text-align: right;">Page 420</p> <p>1 BY MR. KLATT:</p> <p>2 Q. Do you know what that means?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. I understand that using</p> <p>6 whatever the ASTM method, that this finding</p> <p>7 would be considered background levels. I</p> <p>8 don't know if that's the same method that was</p> <p>9 used to test this.</p> <p>10 BY MR. KLATT:</p> <p>11 Q. So just in summary, when you</p> <p>12 cited Julie Pier's Exhibit 47 in your report,</p> <p>13 you can't tell Judge Wilson that any of these</p> <p>14 samples on Exhibit 47 ended up in Johnson &</p> <p>15 Johnson baby powder or Shower to Shower,</p> <p>16 correct?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form, assumes facts not in evidence.</p> <p>19 A. I don't have that information.</p> <p>20 BY MR. KLATT:</p> <p>21 Q. Let me ask you about fragrance.</p> <p>22 Can you rule out fragrance as the sole cause</p> <p>23 of ovarian cancer in women who use talc-based</p> <p>24 body powder products?</p>
<p style="text-align: right;">Page 419</p> <p>1 A. Yes.</p> <p>2 Q. Do you see, for example, the</p> <p>3 very last sample says, "finding</p> <p>4 indistinguishable from background levels</p> <p>5 determined using ASTM method D6620-00"? Do</p> <p>6 you see that?</p> <p>7 A. I see that.</p> <p>8 Q. Do you have any idea what that</p> <p>9 method is?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. Well, it's -- on the left side,</p> <p>13 this says "Transmission Electron Microscope</p> <p>14 Analysis." I don't know if that that's the</p> <p>15 same as ASTM or not.</p> <p>16 BY MR. KLATT:</p> <p>17 Q. But do you understand what it</p> <p>18 means when it says, "Finding</p> <p>19 indistinguishable from background levels</p> <p>20 determined using ASTM method D6620-00"? Do</p> <p>21 you know what --</p> <p>22 MS. O'DELL: Excuse me. Object</p> <p>23 to the form.</p> <p>24</p>	<p style="text-align: right;">Page 421</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I believe that fragrance that's</p> <p>4 in the product is inflammatory and</p> <p>5 irritating. I don't know of any evidence</p> <p>6 that has studied that fragrance on its own,</p> <p>7 as to whether on its own it causes ovarian</p> <p>8 cancer or not, or if it were out of the</p> <p>9 product it would cause ovarian cancer or not.</p> <p>10 All I have is the information on the whole</p> <p>11 product.</p> <p>12 BY MR. KLATT:</p> <p>13 Q. Do you know whether asbestos --</p> <p>14 high levels of asbestos in drinking water</p> <p>15 causes ovarian cancer?</p> <p>16 A. I don't believe that oral</p> <p>17 ingestion has been shown to cause ovarian</p> <p>18 cancer.</p> <p>19 Q. So not any -- just any</p> <p>20 exposures to asbestos cause ovarian cancer,</p> <p>21 correct?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. So what I said was, that I</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 422</p> <p>1 don't think oral ingestion has been shown to</p> <p>2 cause ovarian cancer.</p> <p>3 BY MR. KLATT:</p> <p>4 Q. You're aware that there's been</p> <p>5 studies of drinking -- of ovarian cancer in</p> <p>6 women who consumed high levels of drinking</p> <p>7 water for long periods of time that had high</p> <p>8 levels of asbestos in it, correct?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. Restate that question.</p> <p>12 BY MR. KLATT:</p> <p>13 Q. Yeah, I'm sorry, that was a bad</p> <p>14 question. You're aware there's been studies</p> <p>15 done of women who consumed, over long periods</p> <p>16 of time, drinking water with high levels of</p> <p>17 asbestos in it and had no increased risk of</p> <p>18 ovarian cancer, correct?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. I believe that oral intake of</p> <p>22 asbestos has not been shown to increase the</p> <p>23 risk of ovarian cancer.</p> <p>24</p>	<p style="text-align: right;">Page 424</p> <p>1 BY MR. KLATT:</p> <p>2 Q. Is that Exhibit 10?</p> <p>3 A. It's Exhibit 13. It's here. I</p> <p>4 thought it was here.</p> <p>5 MS. O'DELL: This is my copy.</p> <p>6 What do you have right here?</p> <p>7 THE WITNESS: That's</p> <p>8 Exhibit 13.</p> <p>9 BY MR. KLATT:</p> <p>10 Q. And is 13 the IARC talc</p> <p>11 monograph or the IARC asbestos monograph?</p> <p>12 A. It's the IARC talc one.</p> <p>13 Q. Didn't we mark the -- we did?</p> <p>14 MS. O'DELL: I don't see it.</p> <p>15 MR. SILVER: Let's go off the</p> <p>16 record while we look at the exhibit.</p> <p>17 MS. O'DELL: Well, he's asking</p> <p>18 the questions. We're looking here.</p> <p>19 There's no need to go off the record,</p> <p>20 I don't think.</p> <p>21 MR. SILVER: Mike, let's do it.</p> <p>22 MR. KLATT: Yeah, until we find</p> <p>23 it, let's go off the record, because I</p> <p>24 don't want to waste time looking for</p>
<p style="text-align: right;">Page 423</p> <p>1 BY MR. KLATT:</p> <p>2 Q. Are you aware of any</p> <p>3 nonoccupational studies of women living in</p> <p>4 the vicinity of asbestos mines that show that</p> <p>5 they had an increased risk of ovarian cancer?</p> <p>6 A. I'm not aware of any data</p> <p>7 that -- studies that show that women living</p> <p>8 near mines, that mine asbestos or talcum</p> <p>9 powder have an increased risk of ovarian</p> <p>10 cancer.</p> <p>11 Q. And, in fact, IARC said it</p> <p>12 based its determination that there was a</p> <p>13 potential link between asbestos and ovarian</p> <p>14 cancer based only on cohort studies of high</p> <p>15 occupational exposure in women, correct?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 If you need to look at the IARC</p> <p>19 monograph, Dr. Wolf, we'll pull it</p> <p>20 out.</p> <p>21 A. So the IARC monograph, I know</p> <p>22 that they looked at -- I can't remember what</p> <p>23 -- if this is the right one or the other one.</p> <p>24 Anyway.</p>	<p style="text-align: right;">Page 425</p> <p>1 it. I thought all the exhibits were</p> <p>2 here.</p> <p>3 MS. O'DELL: Are you going to</p> <p>4 mark it?</p> <p>5 MR. KLATT: No, I thought it's</p> <p>6 already marked.</p> <p>7 MS. BROWN: It's already</p> <p>8 marked.</p> <p>9 MS. O'DELL: Look right there.</p> <p>10 THE WITNESS: That's Dr. Saed's</p> <p>11 paper. This is my CV. This is my</p> <p>12 report. What's this one? There it</p> <p>13 is.</p> <p>14 MS. O'DELL: There it is.</p> <p>15 A. I knew it was there.</p> <p>16 BY MR. KLATT:</p> <p>17 Q. Would you look at page 256, and</p> <p>18 let's identify for the record that you're</p> <p>19 looking at Exhibit 10, which is the portion</p> <p>20 of the IARC 2012 monograph dealing with</p> <p>21 asbestos; is that correct?</p> <p>22 A. Yes.</p> <p>23 Q. And you see over in the</p> <p>24 right-hand column of page 256, it says, "The</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 426</p> <p>1 IARC Working Group noted a causal association</p> <p>2 between exposure to asbestos and cancer of</p> <p>3 the ovary was clearly established, based on</p> <p>4 five strongly positive cohort mortality</p> <p>5 studies of women with heavy occupational</p> <p>6 exposure to asbestos."</p> <p>7 Correct?</p> <p>8 A. I see that.</p> <p>9 Q. And do you -- can you flip over</p> <p>10 to page 280 of that asbestos IARC monograph.</p> <p>11 A. I don't have 280. I only go to</p> <p>12 274.</p> <p>13 MS. BROWN: I think your</p> <p>14 counsel has the -- did we give you the</p> <p>15 larger copy?</p> <p>16 MS. O'DELL: You gave me this</p> <p>17 copy. But it -- and it's definitely a</p> <p>18 larger one, but let's see what --</p> <p>19 THE WITNESS: I got it. I got</p> <p>20 page 280.</p> <p>21 MS. BROWN: Here's another one</p> <p>22 if you need another one.</p> <p>23 BY MR. KLATT:</p> <p>24 Q. Actually, that's my highlighted</p>	<p style="text-align: right;">Page 428</p> <p>1 BY MR. KLATT:</p> <p>2 Q. I hand you what's marked as</p> <p>3 Exhibit 22.</p> <p>4 A. Page 280.</p> <p>5 Q. And that is the full 2012 IARC</p> <p>6 asbestos monograph that previously Exhibit 10</p> <p>7 was an excerpt from --</p> <p>8 A. Yes.</p> <p>9 Q. -- is that correct?</p> <p>10 A. That's correct.</p> <p>11 Q. And we established that on</p> <p>12 page 256, they said that the link between</p> <p>13 ovarian cancer and asbestos was based on</p> <p>14 heavy occupational exposure to asbestos in</p> <p>15 women, correct?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 BY MR. KLATT:</p> <p>19 Q. Is that correct?</p> <p>20 A. "The Working Group noted that a</p> <p>21 causal association between exposure and</p> <p>22 cancer in the" -- "to asbestos and cancer of</p> <p>23 the ovary was clearly established, based on</p> <p>24 five strongly positive cohort studies of</p>
<p style="text-align: right;">Page 427</p> <p>1 one. Can I give you this one? I just want</p> <p>2 you to verify that you're looking at the same</p> <p>3 thing that's been marked as Exhibit 10.</p> <p>4 MS. O'DELL: Well, it's</p> <p>5 actually not the same as Exhibit 10,</p> <p>6 because what you provided to her is a</p> <p>7 more comprehensive copy of the</p> <p>8 monograph.</p> <p>9 MR. KLATT: What I provided her</p> <p>10 was the complete asbestos monograph</p> <p>11 that Exhibit 10 is a part of.</p> <p>12 MS. O'DELL: Well, that's my</p> <p>13 point.</p> <p>14 MR. KLATT: Okay.</p> <p>15 MS. O'DELL: It's not the same</p> <p>16 thing. And so just mark it.</p> <p>17 MS. BROWN: Let's just mark it.</p> <p>18 MR. KLATT: Yeah, let's mark</p> <p>19 this as whatever our next exhibit is.</p> <p>20 Do you know what that number</p> <p>21 is?</p> <p>22 (Deposition Exhibit 22 marked</p> <p>23 for identification.)</p> <p>24</p>	<p style="text-align: right;">Page 429</p> <p>1 women with heavy occupational exposure to</p> <p>2 asbestos."</p> <p>3 Yes.</p> <p>4 Q. Now, flip over, if you would,</p> <p>5 to page 280.</p> <p>6 A. Okay. I'm there.</p> <p>7 Q. I believe in the right-hand</p> <p>8 column, this same exact working group, what</p> <p>9 did they say about the relationship between</p> <p>10 talc and ovarian cancer?</p> <p>11 MS. O'DELL: I'm sorry, where</p> <p>12 are you reading, Mike? On 280?</p> <p>13 BY MR. KLATT:</p> <p>14 Q. Do you see --</p> <p>15 MS. O'DELL: Are you reading --</p> <p>16 BY MR. KLATT:</p> <p>17 Q. On page 280, it makes a comment</p> <p>18 about --</p> <p>19 A. They're referencing the IARC</p> <p>20 10.</p> <p>21 Q. Yeah. And what does --</p> <p>22 A. "The association between</p> <p>23 exposure to talc," that one?</p> <p>24 Q. Yes. Can you read that into</p>

108 (Pages 426 to 429)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 430</p> <p>1 the record?</p> <p>2 A. "Potential retrograde</p> <p>3 translocation to the ovarian epithelium and</p> <p>4 the development of ovarian cancer" --</p> <p>5 THE REPORTER: Hold on. You're</p> <p>6 going to have to back up --</p> <p>7 THE WITNESS: Okay.</p> <p>8 A. "The association between</p> <p>9 exposure to talc, potential retrograde</p> <p>10 translocation to the ovarian epithelium and</p> <p>11 the development of ovarian cancer is</p> <p>12 controversial."</p> <p>13 And this is referencing IARC</p> <p>14 2010 and this volume.</p> <p>15 Q. So while the IARC working group</p> <p>16 in 2012 said that asbestos exposure is</p> <p>17 related to ovarian cancer based on heavy</p> <p>18 occupational exposure, this same working</p> <p>19 group said the association between exposure</p> <p>20 to talc, retrograde translocation to the</p> <p>21 ovary and development of ovarian cancer is</p> <p>22 controversial, correct?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p style="text-align: right;">Page 432</p> <p>1 to the ovary, have they?</p> <p>2 A. No. That they're carcinogenic,</p> <p>3 not specifically to the ovary.</p> <p>4 Q. The type of carcinogenicity</p> <p>5 they're referring to with those metals are</p> <p>6 when they're breathed in fumes, correct?</p> <p>7 A. I can't recall.</p> <p>8 Q. Are you aware that chromium is</p> <p>9 an essential trace heavy metal for nutrition?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. I haven't studied nutrition in</p> <p>13 a long time. If I saw a list and saw it on</p> <p>14 there, I can't -- I don't know -- I'm not</p> <p>15 aware of that.</p> <p>16 BY MR. KLATT:</p> <p>17 Q. Chromium's contained in</p> <p>18 multivitamins, isn't it, Dr. Wolf?</p> <p>19 A. I don't know. I don't take</p> <p>20 multivitamins and I don't recommend them to</p> <p>21 my patients.</p> <p>22 Q. Chromium can help control your</p> <p>23 blood sugar, right?</p> <p>24 A. Are you telling me that</p>
<p style="text-align: right;">Page 431</p> <p>1 A. So that was the conclusion of</p> <p>2 the IARC 10 talc --</p> <p>3 BY MR. KLATT:</p> <p>4 Q. And it also refers to the IARC</p> <p>5 2012 asbestos monograph, correct?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 BY MR. KLATT:</p> <p>9 Q. Correct?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. It says "and this volume."</p> <p>13 BY MR. KLATT:</p> <p>14 Q. And this volume is what?</p> <p>15 A. 2012.</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 BY MR. KLATT:</p> <p>19 Q. The -- this volume that you</p> <p>20 just referred to is the 2012 IARC asbestos</p> <p>21 monograph, correct?</p> <p>22 A. That's correct.</p> <p>23 Q. IARC's never said that</p> <p>24 chromium, cobalt or nickel are carcinogenic</p>	<p style="text-align: right;">Page 433</p> <p>1 chromium is released from the pancreas to</p> <p>2 help control blood sugar?</p> <p>3 Q. Do you know what chromium does</p> <p>4 as an essential trace nutrient in the body?</p> <p>5 A. I don't.</p> <p>6 Q. Are you aware of any evidence</p> <p>7 that the chromium levels in the blood or</p> <p>8 tissue of women who use talc-based body</p> <p>9 powder exceeds that in women who never have</p> <p>10 used such products?</p> <p>11 A. I'm not aware that that study</p> <p>12 has been done.</p> <p>13 Q. So you're not aware of any</p> <p>14 evidence of that, correct?</p> <p>15 MS. O'DELL: Objection to the</p> <p>16 form.</p> <p>17 A. I'm not aware that any study</p> <p>18 like that has been performed.</p> <p>19 BY MR. KLATT:</p> <p>20 Q. Are you aware that cobalt is an</p> <p>21 essential part of vitamin B12?</p> <p>22 A. Yes.</p> <p>23 Q. You understand -- you know what</p> <p>24 the Krebs cycle is?</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 434</p> <p>1 A. I do.</p> <p>2 Q. Do you know that cobalt plays a</p> <p>3 vital role in the Krebs cycle in the human</p> <p>4 body?</p> <p>5 A. It's also been shown to be</p> <p>6 carcinogenic, possibly carcinogenic.</p> <p>7 Q. Has IARC ever said that cobalt</p> <p>8 is possibly carcinogenic to the ovaries?</p> <p>9 A. Not specifically to the</p> <p>10 ovaries.</p> <p>11 Q. Are you aware of any evidence</p> <p>12 that the cobalt levels in the blood or tissue</p> <p>13 of women who use talc-based body powder</p> <p>14 exceeds that in the blood or tissues of women</p> <p>15 who have never used such body powders?</p> <p>16 A. I'm not aware of any studies</p> <p>17 that have been done to show that.</p> <p>18 Q. So you're not aware of any such</p> <p>19 evidence, correct?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. I'm not aware of any studies</p> <p>23 that have looked at that.</p> <p>24</p>	<p style="text-align: right;">Page 436</p> <p>1 BY MR. KLATT:</p> <p>2 Q. So you know of no such</p> <p>3 evidence, correct?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. I'm not aware of any</p> <p>7 evidence -- any study that's looked at that</p> <p>8 question.</p> <p>9 BY MR. KLATT:</p> <p>10 Q. Would you agree with me that</p> <p>11 foreign particles, other than talc that had</p> <p>12 nothing to do with talc or talc-based body</p> <p>13 powders, can be introduced into the female</p> <p>14 reproductive tract by the activities you</p> <p>15 listed earlier, intercourse, going to the</p> <p>16 bathroom, toilet paper, riding a bike,</p> <p>17 exercising, use of tampons, walking, all</p> <p>18 those activities can introduce non-talc</p> <p>19 foreign particles into the reproductive</p> <p>20 tract?</p> <p>21 A. If they're exposed to the</p> <p>22 perineal tissue, they could.</p> <p>23 Q. Are you aware that pathologists</p> <p>24 hired by these plaintiffs' lawyers have found</p>
<p style="text-align: right;">Page 435</p> <p>1 BY MR. KLATT:</p> <p>2 Q. Are you aware that nickel is</p> <p>3 found in nuts, dried beans, peas, soybeans,</p> <p>4 grains and chocolate?</p> <p>5 A. I'm not aware of that.</p> <p>6 Q. Are you aware that nickel is</p> <p>7 found in some multivitamins?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. I don't look at the list of</p> <p>11 multivitamins, so I'm going to say I don't</p> <p>12 know.</p> <p>13 BY MR. KLATT:</p> <p>14 Q. Can you tell Judge Wolfson of</p> <p>15 any evidence you know of, that the levels of</p> <p>16 nickel in the blood or tissues of women who</p> <p>17 use talc-based body powders exceeds that in</p> <p>18 the blood or tissues of women who have never</p> <p>19 used such products?</p> <p>20 A. I'm not --</p> <p>21 MS. O'DELL: Excuse me. Object</p> <p>22 to the form.</p> <p>23 A. I'm not aware that any study of</p> <p>24 that nature has been performed.</p>	<p style="text-align: right;">Page 437</p> <p>1 hundreds of foreign particles that have</p> <p>2 nothing to do with talc-based body powders in</p> <p>3 the tissues of women who have ovarian cancer?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 A. I'm not aware of that</p> <p>7 information.</p> <p>8 BY MR. KLATT:</p> <p>9 Q. Would that surprise you?</p> <p>10 A. It would not surprise me.</p> <p>11 Q. Why?</p> <p>12 A. Because I have multiple levels</p> <p>13 of evidence that inert particles can go from</p> <p>14 the vagina and reach the upper</p> <p>15 reproductive -- female reproductive tract.</p> <p>16 Q. Do you have any curiosity</p> <p>17 whether any of these inert particles that</p> <p>18 have nothing to do with talc-based body</p> <p>19 powders, might be responsible for</p> <p>20 inflammation that causes ovarian cancer?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 A. If I had any evidence in an</p> <p>24 epidemiologic study or concerns that there's</p>

110 (Pages 434 to 437)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 438</p> <p>1 anything else, I would definitely want it 2 studied. I've never seen an epidemiologic 3 study that suggested that toilet paper or any 4 of those other things you mentioned are 5 potentially associated with an increased risk 6 of ovarian cancer. 7 BY MR. KLATT: 8 Q. Are you aware in the '60s and 9 '70s, that tampons contained asbestos? 10 A. I wasn't aware of that. 11 MS. O'DELL: You were not or 12 you were? I'm sorry. 13 THE WITNESS: Was not. 14 BY MR. KLATT: 15 Q. Have you investigated -- had 16 any curiosity about investigating the 17 non-talc-based body powder particles that 18 women's reproductive tracts may be exposed to 19 that can result in ovarian cancer? 20 MS. O'DELL: Object to the 21 form. 22 A. I don't have any evidence that 23 there's anything else that's been suggested 24 that something else could cause ovarian</p>	<p style="text-align: right;">Page 440</p> <p>1 A. Most of it's eliminated out of 2 the body. In the vast majority of women, 3 some of it goes retrograde. 4 Q. And you talked about 5 endometriosis earlier, correct? 6 A. Yes. 7 Q. That's endometrial tissue 8 that's already in the uterus that may get 9 into the peritoneum, correct? 10 MS. O'DELL: Objection. 11 A. It's endometrial tissue that 12 during the time of menstruation goes back out 13 through the fallopian tubes and goes -- it 14 can go in the ovaries, in the pelvis, 15 anywhere in the abdomen. I've seen it in the 16 chest. 17 BY MR. KLATT: 18 Q. But that endometrial tissue 19 starts in the uterus, correct? 20 A. That's correct. 21 Q. That's halfway up the 22 reproductive tract to the ovaries, correct? 23 A. That's in the uterus. 24 Q. You're not aware of any sort of</p>
<p style="text-align: right;">Page 439</p> <p>1 cancer, that's introduced through the 2 perineum. 3 BY MR. KLATT: 4 Q. People just haven't looked at 5 it, correct? 6 MS. O'DELL: Object to the 7 form. 8 A. Generally, people look at a 9 question when they see something that happens 10 that suggests that there may be a 11 correlation. 12 BY MR. KLATT: 13 Q. But there's lots of things that 14 can cause cancer that haven't been studied 15 yet, correct? 16 MS. O'DELL: Object to the 17 form. 18 A. I don't know the answer to 19 that. 20 BY MR. KLATT: 21 Q. You would agree with me, that 22 during a woman's reproductive years, every 23 month she sheds the lining of her uterus and 24 it's eliminated out of the body, correct?</p>	<p style="text-align: right;">Page 441</p> <p>1 endometrial tissue coming from the external 2 genital area, moving up the vagina, across 3 the cervix into the uterus, correct? 4 A. Well, there isn't any 5 endometrial tissue in the vagina or the 6 cervix. 7 Q. That's my point. The tissue in 8 endometriosis starts in the uterus, correct? 9 A. Yes. 10 Q. The talc particles that women 11 apply when they apply talc, are applied 12 externally, correct? 13 A. That's correct. 14 Q. Okay. And so they're nowhere 15 near the uterus when they're applied, 16 correct? 17 MS. O'DELL: Object to the 18 form. 19 A. Define "near." 20 BY MR. KLATT: 21 Q. They're on the external genital 22 area, correct? 23 A. They're on the external genital 24 area.</p>

111 (Pages 438 to 441)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 442</p> <p>1 Q. And they have the entire 2 vaginal canal between the external genital 3 area and then the cervix, correct? 4 A. Correct. 5 Q. And then they have to cross the 6 cervix, correct? 7 A. Yeah. 8 Q. Before they even get to the 9 uterus, correct? 10 A. That's correct. 11 Q. And they're still not to the 12 fallopian tubes or ovaries, right? 13 A. That's correct. 14 Q. And I understand that you 15 testified earlier today, that you don't know 16 of a single study that traced talc particles 17 placed externally and traced them up the 18 vaginal canal, across the cervix, through the 19 uterus, up the fallopian tubes to the 20 ovaries, correct? 21 MS. O'DELL: Object to the 22 form. 23 A. I'm aware of multiple studies 24 of other inert products that cross from the</p>	<p style="text-align: right;">Page 444</p> <p>1 THE VIDEOGRAPHER: Going off 2 the record. The time is 5:51 p.m. 3 (Recess taken from 5:51 p.m. to 4 5:52 p.m.) 5 THE VIDEOGRAPHER: Back on the 6 record. The time is 5:52 p.m. 7 BY MR. KLATT: 8 Q. Dr. Wolf, just a quick question 9 about your CV. I just want to make sure I'm 10 clear. Have you ever held the position of 11 full professor at an institution? 12 A. Yes. 13 Q. Okay. I just wasn't sure. And 14 that's listed on your CV; is that correct? 15 A. Yes. 16 Q. And are you still holding a 17 full professorship, or did you give that up 18 at some point? 19 A. I gave that up. 20 Q. When was that? 21 A. When I left Banner MD Anderson 22 in 2014. I haven't had an academic position 23 since then. 24 Q. And earlier, you said that you</p>
<p style="text-align: right;">Page 443</p> <p>1 genital area -- or the vagina, into the 2 ovaries and the pelvis. As -- since other 3 inert substances do cross that way, it makes 4 sense to me that talc or something else, 5 other things that we talked about, certainly 6 could also. 7 BY MR. KLATT: 8 Q. But none of those particles 9 that you just referred to were applied 10 externally, correct? 11 A. They were not applied 12 externally. 13 Q. And talc is, correct? 14 A. And talc is. But the vagina is 15 open to the outside. 16 Q. Any foreign particle, not just 17 talc? 18 A. Excuse me. Yes. Yes. 19 MR. KLATT: Can we go off the 20 record for just a second. I think I 21 have little, if anything, left. 22 MS. O'DELL: Okay. 23 MR. KLATT: I just want to look 24 through my notes real quick.</p>	<p style="text-align: right;">Page 445</p> <p>1 had seen inflammation when you operated on 2 women with ovarian cancer, I think? 3 MS. O'DELL: Object to form. 4 A. I have seen pathologic slides. 5 I look at all the slides of my patients with 6 ovarian cancer. And sometimes you see 7 inflammation in relationship with the cancer. 8 BY MR. KLATT: 9 Q. And cancer itself is capable of 10 causing inflammation, correct? 11 A. Cancer itself can cause 12 inflammation. 13 MR. KLATT: I think that's all 14 the questions I have. 15 MS. O'DELL: Let's go off the 16 record. 17 THE VIDEOGRAPHER: Going off 18 the record. The time is 5:54 p.m. 19 (Recess taken from 5:54 p.m. to 20 6:16 p.m.) 21 THE VIDEOGRAPHER: Back on the 22 record. The time is 6:16 p.m. 23 24</p>

112 (Pages 442 to 445)

Judith K. Wolf, M.D.

Page 446	Page 448
<p>1 EXAMINATION</p> <p>2 BY MS. O'DELL:</p> <p>3 Q. Dr. Wolf, just a few questions</p> <p>4 for you. You were shown two exhibits today,</p> <p>5 Exhibit 20 and Exhibit 21, from a website</p> <p>6 from a company that you were formerly</p> <p>7 employed by. Do you recall those questions</p> <p>8 and exhibits?</p> <p>9 A. Yes.</p> <p>10 Q. And have you had an opportunity</p> <p>11 to review these documents?</p> <p>12 A. Yes.</p> <p>13 Q. And is there anything that's</p> <p>14 contained in the materials that you -- that</p> <p>15 are in these documents that's inaccurate?</p> <p>16 A. No.</p> <p>17 Q. Is there anything about what</p> <p>18 was written here that's inconsistent with any</p> <p>19 of the opinions that you've given in this</p> <p>20 litigation?</p> <p>21 A. No.</p> <p>22 Q. And in terms of the risk</p> <p>23 factors that you touched on in either of</p> <p>24 these two articles, are there any risk</p>	<p>1 Q. And J&J counsel purported to --</p> <p>2 or suggested that FDA's testing of talcum</p> <p>3 powder products, including J&J's talc, had</p> <p>4 resulted in a finding that there was no</p> <p>5 asbestos in baby powder. Do you recall that?</p> <p>6 MS. BROWN: Objection to the</p> <p>7 form.</p> <p>8 A. I recall that.</p> <p>9 BY MS. O'DELL:</p> <p>10 Q. All right. If you'll turn over</p> <p>11 to page 2 of Exhibit 9, did the FDA state</p> <p>12 that the testing that they performed was</p> <p>13 evidence that there was no asbestos in</p> <p>14 cosmetic talc?</p> <p>15 A. Under the results of the FDA</p> <p>16 survey and what they mean, it says they found</p> <p>17 no asbestos fibers or structures in any of</p> <p>18 the samples that they tested, to shorten it</p> <p>19 out. But the results were limited, because</p> <p>20 only four talc suppliers submitted samples,</p> <p>21 and by the number of products tested. The</p> <p>22 next sentence says, "While the FDA finds</p> <p>23 these results informative, they do not prove</p> <p>24 that most or all talc or talc-containing</p>
Page 447	Page 449
<p>1 factors other than family history or</p> <p>2 familial-related risk factors?</p> <p>3 A. In the "How to find the best</p> <p>4 doctor for ovarian cancer" article, I talk</p> <p>5 about familial risk factors, but don't list</p> <p>6 any of the other ones.</p> <p>7 Q. I'm sorry. So you don't</p> <p>8 address lifestyle risk factors such as --</p> <p>9 A. I don't.</p> <p>10 Q. -- as talc or any others?</p> <p>11 A. Or other hormonal risk factors</p> <p>12 or anything else.</p> <p>13 Q. You've talked today about</p> <p>14 talcum powder products. When you've referred</p> <p>15 to talcum powder products, what did you mean</p> <p>16 in your testimony?</p> <p>17 A. Johnson & Johnson baby powder</p> <p>18 and Shower to Shower.</p> <p>19 Q. You also were given a document</p> <p>20 by counsel for J&J. It was Exhibit No. 9.</p> <p>21 It's got a title and it says "Talc." It's</p> <p>22 from the FDA website. Do you have that in</p> <p>23 front of you?</p> <p>24 A. I do.</p>	<p>1 cosmetic products currently marketed in the</p> <p>2 United States are likely to be free of</p> <p>3 asbestos contamination."</p> <p>4 Q. J&J's counsel didn't read that</p> <p>5 sentence to you, did she?</p> <p>6 MS. BROWN: Objection to the</p> <p>7 form.</p> <p>8 A. No.</p> <p>9 BY MS. O'DELL:</p> <p>10 Q. You were also shown a -- what's</p> <p>11 called a PDQ from the National Cancer</p> <p>12 Institute website, Exhibit 18. Do you have</p> <p>13 that in front of you?</p> <p>14 A. I have it.</p> <p>15 Q. And you were asked questions</p> <p>16 about the section that dealt with talc. Do</p> <p>17 you recall that?</p> <p>18 A. Yes.</p> <p>19 Q. And if you'll turn to page 12</p> <p>20 and 13 of 18, there's a section on perineal</p> <p>21 talc exposure.</p> <p>22 A. Yes.</p> <p>23 Q. And what are the references</p> <p>24 that are cited in that section? What numbers</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 450</p> <p>1 are they?</p> <p>2 A. The reference are numbers 41,</p> <p>3 42, 43, 44 and 45.</p> <p>4 Q. Do you need some water?</p> <p>5 A. Yeah, I need some more.</p> <p>6 Q. And if you'll turn to page 16</p> <p>7 of 18 of Exhibit 18, you'll see it lists</p> <p>8 there references 41 through 45.</p> <p>9 A. Yes.</p> <p>10 Q. And do those appear to be the</p> <p>11 references that the authors at NCI relied on</p> <p>12 in reaching their opinions regarding perineal</p> <p>13 talc use?</p> <p>14 A. Yes.</p> <p>15 Q. And do those include -- excuse</p> <p>16 me. Do those references include the broad</p> <p>17 cross section of evidence that you reviewed</p> <p>18 and considered in reaching your opinions in</p> <p>19 this case?</p> <p>20 MS. BROWN: Objection to the</p> <p>21 form.</p> <p>22 A. No.</p> <p>23 BY MS. O'DELL:</p> <p>24 Q. Are at least two of the five</p>	<p style="text-align: right;">Page 452</p> <p>1 experts regarding the appropriate methodology</p> <p>2 for testing asbestos in talc?</p> <p>3 MS. BROWN: Objection to the</p> <p>4 form.</p> <p>5 A. I would refer to other experts</p> <p>6 in that area.</p> <p>7 BY MS. O'DELL:</p> <p>8 Q. Would you -- would you defer</p> <p>9 to -- back up just a second.</p> <p>10 You were asked questions about</p> <p>11 Dr. Longo and Rigler's report in the MDL.</p> <p>12 A. Yes.</p> <p>13 Q. And you recall in Dr. Longo and</p> <p>14 Rigler's report, that they do perform a</p> <p>15 quantification or an estimate of the number</p> <p>16 of fibers in a particular bottle if there's a</p> <p>17 positive test. Do you recall those?</p> <p>18 A. Yes.</p> <p>19 MS. BROWN: Objection to the</p> <p>20 form.</p> <p>21 BY MS. O'DELL:</p> <p>22 Q. Would you defer to Dr. Longo</p> <p>23 and Dr. Rigler on calculations like that, in</p> <p>24 terms of the specific composition of a</p>
<p style="text-align: right;">Page 451</p> <p>1 references in early 2000s, I think 2000 and</p> <p>2 2003?</p> <p>3 A. 2003, 2013. Schildkraut, which</p> <p>4 is the newest one that they just added, 2016,</p> <p>5 2000, 2014.</p> <p>6 Q. Yes. And the references</p> <p>7 included here certainly do not cover all the</p> <p>8 material that you reviewed, considered,</p> <p>9 relied on in reaching your opinion, including</p> <p>10 other meta-analyses, the mechanistic data, et</p> <p>11 cetera?</p> <p>12 A. They do not include all of the</p> <p>13 data that I considered, and the most recent</p> <p>14 data that's even mentioned, as I said, is the</p> <p>15 2016 Schildkraut study.</p> <p>16 Q. Put that aside.</p> <p>17 You were asked a number of</p> <p>18 questions about asbestos testing, the type of</p> <p>19 testing, the methodology, whether it was</p> <p>20 transmission electron microscope or XRD, I</p> <p>21 think was asked of you. Do you recall those</p> <p>22 series of questions?</p> <p>23 A. I do.</p> <p>24 Q. And would you defer to other</p>	<p style="text-align: right;">Page 453</p> <p>1 specific bottle?</p> <p>2 MS. BROWN: Objection to the</p> <p>3 form.</p> <p>4 A. Yes.</p> <p>5 BY MS. O'DELL:</p> <p>6 Q. As a GYN oncologist,</p> <p>7 gynecologic oncologist, that's not something</p> <p>8 that you're offering opinions on or that</p> <p>9 would be within your expertise, correct?</p> <p>10 MS. BROWN: Form.</p> <p>11 A. That's not something I'm</p> <p>12 offering opinions on or is within my area of</p> <p>13 expertise.</p> <p>14 BY MS. O'DELL:</p> <p>15 Q. Okay. And you would not --</p> <p>16 would defer to Dr. Longo and Dr. Rigler on</p> <p>17 that point?</p> <p>18 A. I would refer to Dr. Longo and</p> <p>19 Dr. Rigler.</p> <p>20 Q. And in regard to questions you</p> <p>21 received about geology or deposits, talc</p> <p>22 deposits, would you defer to experts in</p> <p>23 geology on those particular matters?</p> <p>24 A. Yes.</p>

Judith K. Wolf, M.D.

Page 454	Page 456
<p>1 MS. BROWN: Form.</p> <p>2 MS. O'DELL: I don't know what</p> <p>3 the form objection is, but let me see</p> <p>4 if I can address it.</p> <p>5 BY MS. O'DELL:</p> <p>6 Q. Dr. Wolf, would you defer to</p> <p>7 geology experts in terms of the composition</p> <p>8 of the particular talc ore deposit?</p> <p>9 A. A talc deposit?</p> <p>10 Q. Yes.</p> <p>11 A. Yes.</p> <p>12 Q. You were also asked by</p> <p>13 Mr. Klatt about adhesions and inflammation,</p> <p>14 acute inflammation following a surgical</p> <p>15 procedure. Is there any evidence -- any</p> <p>16 suggestion that acute inflammation following</p> <p>17 a surgical procedure causes ovarian cancer?</p> <p>18 A. No.</p> <p>19 Q. Let me -- you were asked some</p> <p>20 questions about the IARC monograph, Volume</p> <p>21 93, the 2010 monograph. It was marked as</p> <p>22 Exhibit 13.</p> <p>23 A. This one. Yes.</p> <p>24 Q. And, Dr. Wolf, was IARC's</p>	<p>1 the literature, the totality of the evidence,</p> <p>2 can platy talc cause inflammation?</p> <p>3 A. Yes.</p> <p>4 Q. Does inflammation in the ovary</p> <p>5 cause ovarian cancer?</p> <p>6 A. Chronic inflammation in the</p> <p>7 ovary can cause changes that are associated</p> <p>8 with ovarian cancer, yes. Chronic</p> <p>9 inflammation can -- in the ovary can cause</p> <p>10 ovarian cancer.</p> <p>11 Q. You asked a number of questions</p> <p>12 about asbestos and -- in terms of studies</p> <p>13 involving millers and miners. Would you</p> <p>14 explain to what ultimately would be a jury,</p> <p>15 but initially will be Judge Wolfson, what the</p> <p>16 possible routes of exposure are for, you</p> <p>17 know, asbestos and fibrous talc reaching the</p> <p>18 ovary in the context of talcum powder</p> <p>19 products?</p> <p>20 MS. BROWN: Objection to the</p> <p>21 form.</p> <p>22 A. So the possible routes are from</p> <p>23 the perineum, through the open vagina and</p> <p>24 open cervix and open fallopian tubes to the</p>
Page 455	Page 457
<p>1 examination of talc at the time they looked</p> <p>2 at it in 2006, I believe it was, were they</p> <p>3 considering talc containing asbestiform</p> <p>4 fibers?</p> <p>5 MR. KLATT: Objection, form.</p> <p>6 BY MS. O'DELL:</p> <p>7 Q. Let me just ask -- let me ask</p> <p>8 you a different way, see if I can address the</p> <p>9 objection.</p> <p>10 Why don't you turn to page 277,</p> <p>11 please. And, Dr. Wolf, what is the substance</p> <p>12 that the IARC working group is considering in</p> <p>13 the 2010 monograph?</p> <p>14 A. Talc not containing asbestos</p> <p>15 foreign fibers.</p> <p>16 Q. In other words, the 2010</p> <p>17 monograph purported not to address talc with</p> <p>18 asbestos?</p> <p>19 MS. BROWN: Objection, form.</p> <p>20 MR. KLATT: Objection, form.</p> <p>21 A. To investigate what they</p> <p>22 thought or assumed was pure platy talc.</p> <p>23 BY MS. O'DELL:</p> <p>24 Q. Is -- based on your review of</p>	<p>1 ovaries. From inhalation, smaller particles</p> <p>2 can be -- cross the membrane, be absorbed by</p> <p>3 the stroma, get into the lymphatic or blood</p> <p>4 system and get it that way. Fibrous</p> <p>5 particles can pierce the lung in the diagram</p> <p>6 and get into the perineal cavity that way.</p> <p>7 BY MS. O'DELL:</p> <p>8 Q. And is -- are those opinions</p> <p>9 you've just expressed supported by the data</p> <p>10 in the IARC monograph, the 2012 monograph?</p> <p>11 A. Yes.</p> <p>12 MR. KLATT: Objection, form.</p> <p>13 BY MS. O'DELL:</p> <p>14 Q. And did IARC conclude that when</p> <p>15 asbestos and fibrous talc reached the</p> <p>16 ovaries, they can cause ovarian cancer?</p> <p>17 A. Yes.</p> <p>18 Q. And IARC concluded that</p> <p>19 asbestos and fibrous talc were known human</p> <p>20 carcinogens?</p> <p>21 A. Yes.</p> <p>22 Q. You were asked a number of</p> <p>23 questions about whether asbestos was</p> <p>24 necessary in order to reach your opinions</p>

115 (Pages 454 to 457)

Judith K. Wolf, M.D.

Page 458	Page 460
<p>1 about talcum powder products causing ovarian 2 cancer. You recall those questions? 3 A. Yes. 4 Q. And is asbestos, as a component 5 of talcum powder products, essential in order 6 for talcum powder, baby powder and Shower to 7 Shower causing ovarian cancer? 8 MS. BROWN: Objection to the 9 form of the question. 10 A. So a talcum powder product has 11 all of these substance and I assessed it as a 12 whole. Multiple of the substances are either 13 known to be carcinogenic or other substances 14 possibly carcinogenic or fragrances 15 irritating and inflammatory. I looked at the 16 product as a whole. 17 BY MS. O'DELL: 18 Q. If -- and you -- and in doing 19 that, looking at the product as a whole, was 20 it important to you to consider whether there 21 was a potent carcinogen such as asbestos in 22 the product? 23 MS. BROWN: Form. 24 A. It was information that added</p>	<p>1 MS. BROWN: Objection to the 2 form of the question. 3 BY MS. O'DELL: 4 Q. And did Dr. Longo find that 5 there was fibrous talc present in 41 out of 6 42 samples? 7 MS. BROWN: Objection. 8 A. She found fibrous talc in 41 of 9 42 samples. 10 THE REPORTER: Hold on a 11 second. I'm not hearing -- 12 THE WITNESS: I'm sorry. 13 A. She -- 14 MS. BROWN: I -- sorry. Go 15 ahead. 16 A. She found fibrous talc in 41 17 of -- 18 MS. BROWN: He. 19 A. He. I keep picturing a woman. 20 Fibrous talc in 41 of 42 samples. 21 MS. BROWN: And, Doctor, if you 22 wouldn't mind just giving me second to 23 object before you start answering -- 24 THE WITNESS: I'm sorry.</p>
Page 459	Page 461
<p>1 to my concerns about the product. But 2 knowing that platy talc can cause 3 inflammation and is possibly carcinogenic, as 4 per IARC, and that platy talc appears to be 5 almost universally, as per Longo's testing, 6 part of talcum powder product, 41 out of 42 7 samples that she tested, and that fibrous 8 talc is asbestos, a form of asbestos, the 9 other asbestos fibers, one way or the other, 10 just add to my concern. 11 BY MS. O'DELL: 12 Q. Yeah. You -- and just when you 13 were relying, I think you misspoke. You were 14 saying the 41 out of 42 samples in 15 Dr. Longo's testing and you referred to platy 16 talc. Did you mean to say that? 17 MS. BROWN: Objection to the 18 form. 19 A. No, I meant fibrous talc. 20 BY MS. O'DELL: 21 Q. And Dr. Longo tested Johnson & 22 Johnson historical samples for the presence 23 of fibrous talc? 24 A. That's correct.</p>	<p>1 MS. BROWN: -- it will make the 2 court reporter's job easier. 3 THE WITNESS: Sorry. 4 BY MS. O'DELL: 5 Q. And if you pulled any one 6 component that you've talked about today out 7 of the talcum powder products, would that 8 change your opinions? 9 A. No. 10 MS. O'DELL: That's all I have, 11 Dr. Wolf. Thank you. 12 MS. BROWN: Go off? 13 MR. KLATT: Yeah. 14 MS. BROWN: Can we go off for 15 one second? 16 THE VIDEOGRAPHER: Going off 17 the record. The time is 6:36 p.m. 18 (Recess taken from 6:36 p.m. to 19 6:44 p.m.) 20 THE VIDEOGRAPHER: Back on the 21 record. The time is 6:44 p.m. 22 FURTHER EXAMINATION 23 BY MS. BROWN: 24 Q. Dr. Wolf, you were just asked</p>

116 (Pages 458 to 461)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 462</p> <p>1 some questions by counsel for plaintiffs 2 regarding Exhibits 20 and 21, articles that 3 you authored regarding ovarian cancer. Do 4 you recall those questions? 5 A. Yes. 6 Q. Okay. And you'd agree with me 7 that over the course of your career, you have 8 authored a number of articles, both in the 9 medical press and in the popular press, 10 regarding ovarian cancer, correct? 11 A. Yes. 12 Q. And you have never, over the 13 course of your entire career, published the 14 opinion that talc causes ovarian cancer, 15 correct? 16 A. I have not. 17 Q. And you have never, over the 18 course of your career, blogged or tweeted or 19 posted anything on any of the social media 20 accounts where you have a presence, that talc 21 causes ovarian cancer, correct? 22 A. I have not. 23 Q. And you have never spoken at 24 any symposia or conference and offered the</p>	<p style="text-align: right;">Page 464</p> <p>1 was in her testing. I don't remember the 2 word "quantification of asbestos." 3 BY MS. BROWN: 4 Q. So you are relying on 5 Dr. Longo's testing for how much asbestos is 6 in baby powder? 7 A. To interpret her findings. 8 MS. O'DELL: His findings. 9 A. His findings. I'm trying to 10 make Dr. Longo a woman. It's not working. 11 BY MS. BROWN: 12 Q. You -- in sitting here -- and 13 when you offered your opinion in this case, 14 though, you didn't have in mind a certain 15 amount of asbestos that was needed or found 16 in the baby powder to cause ovarian cancer, 17 right? 18 MS. O'DELL: Object to the 19 form. 20 A. Any amount of asbestos in baby 21 talcum powder product, I'm concerned about 22 causing ovarian cancer. 23 BY MS. BROWN: 24 Q. And if I understood your</p>
<p style="text-align: right;">Page 463</p> <p>1 opinion that talc causes ovarian cancer, 2 correct? 3 MS. O'DELL: Object to the 4 form. It's already been covered 5 previously today. 6 MS. BROWN: Form is the 7 objection. 8 A. Not that I recall. 9 BY MS. BROWN: 10 Q. You were asked some questions 11 regarding the work of Dr. Longo and 12 Dr. Rigler. Do you recall those? 13 A. Yes. 14 Q. And I assume you have not met 15 Dr. Longo; is that correct? 16 A. No, I have not. 17 Q. Okay. And you told counsel for 18 plaintiffs, that you are relying on 19 Dr. Longo's quantification of asbestos. Was 20 that your testimony? 21 MS. O'DELL: Object to the 22 form. 23 A. Quantification of -- to 24 understand how much of the -- what she found</p>	<p style="text-align: right;">Page 465</p> <p>1 testimony to plaintiffs' lawyer earlier, if 2 you took asbestos -- the asbestos that you 3 think is in baby powder, if you took it out, 4 you would still hold the opinion that baby 5 powder causes ovarian cancer; is that right? 6 A. Yes. 7 Q. And, in fact, that's your 8 opinion as it relates to any of the 9 components of baby powder that you believe 10 exists, such as platy talc, fibrous talc, 11 asbestos, heavy metals and fragrances, 12 correct? 13 MS. O'DELL: Object to the 14 form. 15 A. If I took any one of those out, 16 I think that talcum powder products would 17 still cause ovarian cancer. 18 BY MS. BROWN: 19 Q. And what if you took two out of 20 the five out, would you still hold the 21 opinion that powder products cause ovarian 22 cancer? 23 MS. O'DELL: Object to the 24 form, incomplete hypothetical.</p>

Judith K. Wolf, M.D.

Page 466	Page 468
<p>1 A. If you took any one of them 2 out, I would still have the opinion that 3 talcum powder product causes ovarian cancer. 4 I don't know how you can take all of them out 5 and still have a talcum powder product. 6 BY MS. BROWN: 7 Q. Well, you understand that there 8 is -- talcum powder exists that does not 9 include fragrances, heavy metals, asbestos 10 and fibrous talc. Do you have that 11 understanding? 12 MS. O'DELL: Object to the 13 form. 14 A. I'm not sure that there's 15 talcum powder that doesn't have at least 16 fibrous talc. 17 BY MS. BROWN: 18 Q. And so are you of the opinion 19 that platy talc and fibrous talc alone cause 20 ovarian cancer? 21 MS. O'DELL: Object to the 22 form. 23 A. I'm of the opinion that talcum 24 powder product contains all of those</p>	<p>1 A. There isn't epidemiology 2 because -- because I don't know that the 3 talcum powder product in the epidemiology 4 left any of those out. 5 Q. So you issued a multipage 6 report in this case, right, Dr. Wolf? 7 A. Yes. 8 Q. And that report contains 9 numerous cites to epidemiology that looked at 10 people using cosmetic talcum powder, correct? 11 A. That's correct. 12 Q. Is it your testimony here today 13 that none of that epidemiology informs your 14 opinion about Johnson & Johnson baby powder 15 products? 16 A. That is not -- 17 MS. O'DELL: Excuse me. 18 A. -- my opinion. 19 MS. O'DELL: Object to the 20 form, misstates her testimony. 21 A. What my understanding of your 22 question was is, do I have epidemiologic 23 studies that show that if one -- any one of 24 those substances is left out of the product,</p>
Page 467	Page 469
<p>1 ingredients that we list and that it causes 2 ovarian cancer. 3 BY MS. BROWN: 4 Q. I'm with you on that. What I 5 want to know is, are you of the opinion that 6 platy talc and fibrous talc alone cause 7 ovarian cancer? 8 A. I'm of the opinion that platy 9 talc can cause cancer and fibrous talc is 10 considered a form of asbestos and can cause 11 cancer. And that those are two of the 12 products in talcum powder product, two of the 13 substances in talcum powder product. 14 I don't know of any evidence 15 that the product doesn't have all of the 16 substances that I've described, and I don't 17 know that I can make an opinion that says if 18 it just had this and this, it would or would 19 not cause cancer. 20 Q. And for your opinion, that if 21 you pulled out any one component of the 22 powder products, the product would still 23 cause ovarian cancer, do you rely on the same 24 epidemiology?</p>	<p>1 that it causes ovarian cancer. And what my 2 answer is, is that my understanding is that 3 all of the epidemiologic studies are looking 4 at the product as I understand it and so I 5 can't give -- I cannot refer to a study that 6 has the product without one of those. 7 BY MS. BROWN: 8 Q. And you were asked some 9 questions about the IARC monograph on 10 nonasbestiform talc. Do you remember that? 11 A. Yes. 12 Q. And many, if not most, of the 13 epidemiology studies that you cite in your 14 report are contained and considered within 15 the IARC monograph on nonasbestiform talc. 16 True? 17 MS. O'DELL: Object to the 18 form. 19 A. I believe that's not true 20 because the -- again, this was 2010 and many 21 of the references that I report are after 22 this was published and they were only 23 reviewing up to 2006 or 2007 when they wrote 24 this.</p>

118 (Pages 466 to 469)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 470</p> <p>1 BY MS. BROWN: 2 Q. Sure. And for studies that 3 looked at talcum powder products prior to 4 2010, you have considered and relied on those 5 in your report as well? 6 A. Yes. 7 Q. And, in fact, the Penninkilampi 8 meta-analysis that you regard as high 9 quality, includes a majority of studies that 10 were considered by the IARC group in 2006, 11 correct? 12 MS. O'DELL: Object to the 13 form. 14 A. It definitely includes some of 15 those older studies. 16 MS. BROWN: I have no further 17 questions at this time. 18 MR. KLATT: I have a couple 19 more. 20 FURTHER EXAMINATION 21 BY MR. KLATT: 22 Q. Can you pull out Exhibit 9, 23 Dr. Wolf. 24 A. Exhibit 9, yes.</p>	<p style="text-align: right;">Page 472</p> <p>1 A. That's correct. 2 Q. Have you ever recommended to a 3 patient of yours who does not have ovarian 4 cancer yet, that she have her ovaries removed 5 because of long-term talc use? 6 A. No. 7 Q. Would you make that 8 recommendation in the future? 9 A. It would be a discussion that I 10 would have with the patient. Looking at all 11 of her risk factors, if her only risk factor 12 was talcum powder usage, I would just want 13 her to know that she's at an increased risk 14 and let her make the decision about that. 15 Q. Are you aware of any 16 professional -- 17 MS. O'DELL: Excuse me, Mike. 18 MR. KLATT: I'm sorry. 19 MS. O'DELL: I'm sorry. Were 20 you done, Dr. Wolf? 21 A. I mean, that's a tough 22 question. The challenge is there's no 23 screening for ovarian cancer, right? So if 24 you have someone who's at an increased risk,</p>
<p style="text-align: right;">Page 471</p> <p>1 Q. And Exhibit 9 is the document 2 that Ms. O'Dell discussed with you a few 3 minutes ago, where the FDA around 2009-2010, 4 tested both raw talc and off-the-shelf 5 talc-based body powder products, correct? 6 A. Yes. 7 Q. And I think you read a portion 8 where it said only four talc suppliers had 9 submitted their products to the FDA for 10 testing. Do you recall that? 11 A. Yes. 12 Q. Are you aware that my client, 13 Imerys, was one of the four that did submit 14 their talc for testing? And I'll just tell 15 you, in case you don't know, that Imerys is 16 the successor to Rio Tinto and Luzenac. And 17 are those talcs tested by the FDA in Exhibit 18 9? 19 A. Yes. 20 Q. And what did the FDA find about 21 whether there was asbestos in those talcs? 22 A. No evidence of asbestos. 23 Q. In either the Rio Tinto 24 Minerals/Luzenac America talc, correct?</p>	<p style="text-align: right;">Page 473</p> <p>1 you can't say, well, we'll look at you more 2 often, we'll test you more often. There's no 3 test to find ovarian cancer early. 4 On the other hand, the 5 generally accepted lifetime risk for ovarian 6 cancer to push a doctor to recommend 7 prophylactic surgery removal of the tubes and 8 ovaries, is a 10 percent or greater lifetime 9 risk. 10 BY MR. KLATT: 11 Q. And talc use doesn't confer 12 that level of use, correct? 13 A. It does not. 14 Q. Okay. And you're not aware of 15 any medical professional organization or 16 agency that has ever made the recommendation 17 that women who have used genital talc for a 18 certain period of time should consider having 19 their ovaries and fallopian tubes removed, 20 correct? 21 A. I am not aware of any. 22 Q. Can you show me one single 23 study, case report, case series, any type of 24 study at all, showing that a woman who used</p>

119 (Pages 470 to 473)

Judith K. Wolf, M.D.

Page 474	Page 476
<p>1 Johnson & Johnson baby powder or Shower to</p> <p>2 Shower product, had inflammation of her</p> <p>3 reproductive tract as a result of that</p> <p>4 powder?</p> <p>5 MS. O'DELL: Objection to the</p> <p>6 form.</p> <p>7 A. I can't -- I can't show you a</p> <p>8 paper that shows that.</p> <p>9 BY MR. KLATT:</p> <p>10 Q. You believe that talc can get</p> <p>11 to the ovaries via inhalation, correct?</p> <p>12 A. Yes.</p> <p>13 Q. Are you aware that talc's</p> <p>14 ubiquitous in the environment?</p> <p>15 A. Yes.</p> <p>16 Q. Are you aware that women just</p> <p>17 walking around on city streets can breathe</p> <p>18 talc particles in during the course of their</p> <p>19 life?</p> <p>20 MS. O'DELL: Objection to form.</p> <p>21 A. I'm aware that talc is</p> <p>22 ubiquitous to the environment.</p> <p>23 BY MR. KLATT:</p> <p>24 Q. Which means you can breathe it</p>	<p>1 Q. Sure. You've seen -- you've</p> <p>2 read the IARC monograph, you know in indoor</p> <p>3 air and outdoor air in urban areas, there's</p> <p>4 concentrations of asbestos fibers just in the</p> <p>5 air we breath.</p> <p>6 MS. O'DELL: Objection to form.</p> <p>7 A. I would have to test the air to</p> <p>8 know for sure that there's asbestos fibers in</p> <p>9 the air here.</p> <p>10 BY MR. KLATT:</p> <p>11 Q. You haven't seen that data in</p> <p>12 the IARC monograph that you reviewed?</p> <p>13 A. In this -- about the air in</p> <p>14 this room, no.</p> <p>15 Q. I'm talking about indoor air</p> <p>16 and outdoor area in urban areas. You've seen</p> <p>17 in the IARC monograph, that there's a certain</p> <p>18 quantity of asbestos fibers in that air,</p> <p>19 correct?</p> <p>20 A. There is a certain amount of</p> <p>21 asbestos fibers in the air.</p> <p>22 Q. And so when you breathe that</p> <p>23 air, you can inhale those asbestos fibers</p> <p>24 and, according to you, they can end up in the</p>
Page 475	Page 477
<p>1 in every single breath you take, correct?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. I'm aware that talc is</p> <p>5 ubiquitous to the environment.</p> <p>6 BY MR. KLATT:</p> <p>7 Q. And so since it's ubiquitous in</p> <p>8 the environment and since you take a breath,</p> <p>9 you know, many times a minute, you're</p> <p>10 probably inhaling talc particles every time</p> <p>11 you breath, or at least every minute you</p> <p>12 breath, correct?</p> <p>13 MS. O'DELL: Objection to the</p> <p>14 form.</p> <p>15 A. I don't have evidence to</p> <p>16 support that.</p> <p>17 BY MR. KLATT:</p> <p>18 Q. Well, you -- and you know, for</p> <p>19 example, that there's asbestos fibers in this</p> <p>20 room as we sit here right now, don't you, Dr.</p> <p>21 Wolf?</p> <p>22 MS. O'DELL: Objection to form.</p> <p>23 A. Do I know that for a fact?</p> <p>24 BY MR. KLATT:</p>	<p>1 ovary, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And the same with talc</p> <p>4 particles, correct?</p> <p>5 A. Yes.</p> <p>6 Q. Didn't even necessarily come</p> <p>7 from body powder, correct --</p> <p>8 MS. O'DELL: Objection, form.</p> <p>9 BY MR. KLATT:</p> <p>10 Q. -- just from the environment?</p> <p>11 MS. O'DELL: Objection to the</p> <p>12 form.</p> <p>13 A. You can inhale it from the air</p> <p>14 and it can get to the ovaries.</p> <p>15 BY MR. KLATT:</p> <p>16 Q. How long have you known</p> <p>17 Margaret Thompson, who is sitting here today?</p> <p>18 A. I met her about two -- a little</p> <p>19 over two years ago.</p> <p>20 Q. Okay. You've never seen or</p> <p>21 been referred any patients by her; is that</p> <p>22 correct?</p> <p>23 A. No.</p> <p>24 Q. Have you communicated with any</p>

120 (Pages 474 to 477)

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 478</p> <p>1 of the other plaintiffs' consultants by -- in 2 person, by phone, by e-mail, in any form or 3 fashion at all? 4 A. The only one I spoke with was 5 Dr. Saed. I spoke on the phone with him once 6 about, I'm going to say, a year or so ago. 7 Q. And what was the substance of 8 that conversation? 9 A. It was about his research. I 10 had questions about what he was doing. 11 Q. And what did you ask him? 12 A. I don't recall exactly. 13 Q. Did you keep notes? 14 A. I did not. 15 Q. How long was the phone call? 16 A. I think it was about a half an 17 hour. 18 Q. And when was that phone call? 19 MS. O'DELL: I think she just 20 said. 21 A. I think it was about a year 22 ago. I can see I was standing in Arizona, 23 which meant I was still working for Provista, 24 so it was sometime before I left there.</p>	<p style="text-align: right;">Page 480</p> <p>1 talked a little bit about the fact that he 2 worked in Detroit at Wayne State, where I 3 know the GYN oncologist, and we were friendly 4 about that. I told him I thought his 5 research was interesting and important. That 6 was it. 7 Q. Are any of the Wayne State 8 gynecologic oncologists you know coauthors of 9 Dr. Saed's paper? 10 A. Yes. Dr. Robert Morris. 11 Q. Have you talked to Dr. Morris 12 about this research? 13 A. I haven't spoken with 14 Dr. Morris about anything in a couple of 15 years. 16 Q. Have you communicated in any 17 form or fashion with any governmental 18 agencies about talc and ovarian cancer? 19 A. I have not. 20 Q. Did you keep any notes of your 21 discussion with Dr. Saed? Maybe I asked 22 that. 23 MS. O'DELL: Asked and 24 answered.</p>
<p style="text-align: right;">Page 479</p> <p>1 BY MR. KLATT: 2 Q. Which month would that have 3 been? 4 A. I don't know. 5 Q. When did you leave there? 6 A. My last working day there was 7 October 1st, but I hadn't been to Arizona for 8 months by then. 9 Q. October 1st of? 10 A. 2018. 11 Q. Okay. But you think it was 12 about a year ago that you spoke to him? 13 A. I do. 14 Q. Approximately January of 2018? 15 MS. O'DELL: Objection to form. 16 She's given her best estimate. 17 A. Approximately. 18 BY MR. KLATT: 19 Q. Can you tell me anything else 20 about the substance of what you talked about 21 with Dr. Saed on that phone call? 22 A. I asked him what research he 23 was doing, what he was looking at, what type 24 of cell lines, what was he looking for. We</p>	<p style="text-align: right;">Page 481</p> <p>1 A. I did not. 2 BY MR. KLATT: 3 Q. Did you ask Dr. Saed during 4 that phone call, who was funding his 5 experiments or work that he was doing? 6 A. I don't remember. 7 Q. What prompted that phone call? 8 A. Margaret and I spoke about that 9 he was doing some research and she asked him 10 would it be okay if I talked to him, and so I 11 called him. 12 Q. How long have you been a 13 gynecologic oncologist? 14 A. I finished my fellowship in 15 1995. 16 Q. Had you ever heard of Dr. Saed 17 before your discussion with Margaret 18 Thompson? 19 A. I had not. He's a Ph.D., so 20 it's not necessarily that I would know who he 21 was. 22 Q. Well, you've been an academic 23 gynecologic oncologist for decades, right? 24 A. Yes.</p>

Judith K. Wolf, M.D.

<p style="text-align: right;">Page 482</p> <p>1 Q. You have never once heard of 2 Dr. Saed, correct? 3 A. I had not. 4 MR. KLATT: That's all the 5 questions I have. 6 MS. O'DELL: I just have one 7 question. 8 FURTHER EXAMINATION 9 BY MS. O'DELL: 10 Q. Dr. Wolf, are your opinions in 11 this case contained in your report and in the 12 deposition you've given here today? 13 A. Yes. 14 MS. O'DELL: That's all I have. 15 MS. BROWN: Just one final 16 question to that. 17 FURTHER EXAMINATION 18 BY MS. BROWN: 19 Q. One final question, Doctor. 20 You're not relying on any materials to form 21 your opinion that are not contained in your 22 report or were discussed or marked as 23 exhibits here today, correct? 24 A. My report, no, and my</p>	<p style="text-align: right;">Page 484</p> <p>1 record. 2 THE VIDEOGRAPHER: This 3 concludes the deposition of Dr. Judy 4 Wolf. Going off the record. The time 5 is 7:03 p.m. 6 (Deposition concluded at 7 7:03 p.m.) 8 ----- 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24</p>
<p style="text-align: right;">Page 483</p> <p>1 references, everything that's here today. 2 Nothing else. 3 Q. And for a housekeeping item, 4 are all of the binders on that table to your 5 left, are those documents on Exhibit B of 6 your report? 7 A. Yes. 8 Q. Nothing additional, right? 9 A. Nothing additional. 10 Q. And all of the binders on the 11 table are the references in your report? 12 A. The references and the 13 additional information that we provided 14 today. 15 Q. Okay. So with that, I don't 16 think it's necessary, unless anyone 17 disagrees, to mark all of the binders. 18 MS. BROWN: And I have no 19 further questions. Thanks. 20 MR. KLATT: As long as the 21 binders don't contain any highlighting 22 or notations. 23 THE WITNESS: Nothing. 24 MS. BROWN: We're off the</p>	<p style="text-align: right;">Page 485</p> <p>1 CERTIFICATE 2 3 I, MICHEAL A. JOHNSON, Registered 4 Diplomat Reporter and Certified Realtime 5 Reporter, do hereby certify that prior to the 6 commencement of the examination, JUDITH K. 7 WOLF, M.D. was duly sworn by me to testify to 8 the truth, the whole truth and nothing but 9 the truth. 10 I DO FURTHER CERTIFY that the 11 foregoing is a verbatim transcript of the 12 testimony as taken stenographically by and 13 before me at the time, place and on the date 14 hereinbefore set forth, to the best of my 15 ability. 16 17 I DO FURTHER CERTIFY that I am 18 neither a relative nor employee nor attorney 19 nor counsel of any of the parties to this 20 action, and that I am neither a relative nor 21 employee of such attorney or counsel, and 22 that I am not financially interested in the 23 action. 24 MICHEAL A. JOHNSON, NCRA Registered Diplomat Reporter NCRA Certified Realtime Reporter Certified LiveNote Reporter Dated: January 8, 2019</p>

122 (Pages 482 to 485)

Judith K. Wolf, M.D.

Page 486		Page 488	
1	ACKNOWLEDGMENT OF DEPONENT	1	-----
2		2	LAWYER'S NOTES
3		3	-----
4	I, _____, do	4	PAGE LINE
5	hereby certify that I have read the foregoing	5	_____
6	pages and that the same is a correct	6	_____
7	transcription of the answers given by me to	7	_____
8	the questions therein propounded, except for	8	_____
9	the corrections or changes in form or	9	_____
10	substance, if any, noted in the attached	10	_____
11	Errata Sheet.	11	_____
12		12	_____
13	_____ JUDITH K. WOLF, M.D. DATE	13	_____
14		14	_____
15	Subscribed and sworn to before me this	15	_____
16	_____ day of _____, 20 ____.	16	_____
17	My commission expires: _____	17	_____
18		18	_____
19	Notary Public	19	_____
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Page 487	
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17	_____
18	_____
19	_____
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123 (Pages 486 to 488)

A	418:7	addition 171:13	315:16,21	ago 10:2,14
AACES 7:20	accounts 462:20	178:24 181:12	316:1,24	11:22 31:19,21
abdomen 440:15	accuracy 173:17	235:12,19	318:13,17	45:5 155:4
abdominal	accurate 262:14	additional 40:3	320:21	279:13 282:19
22:12 408:4	371:11	54:4 82:1 90:4	advise 348:3	342:17 389:8
411:3,23	accurately	223:3 244:13	advisory 363:2,4	471:3 477:19
ability 30:10	263:11	287:8,9,23	advocacy 365:1	478:6,22
228:18 300:14	acknowledged	288:13 359:1,2	advocate 55:10	479:12
485:9	254:15	483:8,9,13	63:9	agree 21:12 22:2
able 24:4 56:22	ACKNOWLEDGE...	Additionally	affect 148:11,12	38:14 116:4
57:10 88:6	5:16 486:1	236:4	148:18 207:17	156:3 158:17
132:12 202:4	ACOG 360:13	additive 71:7	African 7:19	187:14 188:13
203:16 266:1	360:17,23	166:4,14 167:3	African-Amer...	189:15,21
289:13 327:17	361:5,10,19	167:5	234:19 235:1	202:19 214:11
abnormalities	362:3 364:19	additivity 167:7	292:10,15,24	217:12 220:7
339:23,24	365:6,20 366:3	address 302:11	293:8,20	220:13 221:23
343:2,3,6	acquired 136:5	364:13 447:8	294:21 296:1	224:2 232:10
344:1	315:16 320:20	454:4 455:8,17	296:12,23	233:12 237:15
abnormality	acted 394:24	addressed 392:5	297:8,18,22	243:12 245:10
339:22	actinolite 117:11	addressing	298:1,18	254:5,12,13
absolutely 17:4	117:13,13	393:8,18	301:13,16	265:6,14
37:6 84:17	118:9	add-on 257:10	302:1,23 303:2	266:14 287:14
85:7 120:17	action 303:7	adequate 273:13	African-Amer...	287:21 296:23
230:15 330:13	304:2 485:12	273:24 276:14	8:10 293:15,17	305:10 311:13
absorbed 457:2	485:13	396:16,23	295:2,10 296:8	315:14,19,20
abstract 36:10	active 49:10,13	397:3,3,11	296:15 328:3	316:16 318:10
219:16	49:16 363:14	adequately	afternoon	319:5 320:24
abstracts 235:3	365:24	204:6	388:17,18	328:21 329:11
235:15	activities 436:14	adhesion 411:7	age 315:18	331:1 332:15
academic	436:18	411:8	316:7 318:18	335:14 344:10
444:22 481:22	actual 95:10	adhesions 23:14	319:5 320:22	350:10,16
accept 396:23	221:1 371:9	25:7 27:2	321:4,15 322:9	353:14 364:7
accepted 36:11	acute 21:1,5	407:17,23	322:11 323:10	368:21 383:16
193:12 221:7	189:22 217:17	408:9,12 409:1	323:19 356:5	385:6 436:10
221:11,19	217:19,23	409:4 411:13	aged 321:21	439:21 462:6
222:11 223:5	218:10,13	411:16,22	agencies 480:18	agreed 132:23
235:14 391:9	305:21 407:3	412:9 413:12	agency 30:9	agrees 281:9
392:3 397:10	408:17 409:2	454:13	32:5 223:11	ahead 11:2
473:5	411:17 454:14	adjusted 310:22	224:5 227:18	89:14 460:15
access 73:6,15	454:16	Administration	473:16	aimed 354:20
73:22 91:20	add 459:10	122:1 126:16	agent 179:19,19	air 476:3,3,5,7,9
155:22	added 71:7 72:9	Administratio...	283:24	476:13,15,18
accommodate	278:13 406:14	124:20 234:9	agents 283:13	476:21,23
11:9	451:4 458:24	admittedly	403:14	477:13
account 196:18	adding 321:20	132:12	ages 321:6,7	al 7:10 8:6,13
311:6 402:9	392:23,23	adulthood	322:24	Alabama 2:5

Alexis 3:2 225:18 alexis.kellert... 3:3 Ali 42:14 358:15 allegedly 209:21 214:13 Allen 2:2 39:16 40:2,5 41:21 42:6 43:14 395:22,24 396:2,9 ALLISON 2:18 allison.brown... 2:19 allowed 289:2 allows 84:21 Ally 9:16 amendment 31:11 America 3:14,18 388:20 471:24 American 7:16 7:19 amount 107:8 108:18 110:2,8 110:17 131:14 151:14,14,14 151:20,23 161:14 166:5,8 181:2,7,9,20 183:11,18,21 190:16,23 191:1 219:8 220:23 254:24 257:2 295:16 295:17 325:13 327:8,24 332:24 335:15 335:18,22,23 335:24 336:11 336:23 337:3,4 374:20 375:20 375:21 386:7 386:17 464:15 464:20 476:20	amounts 169:6 347:16 377:5 409:7 analysis 202:3 239:3 247:8 248:3 258:18 258:19 261:18 261:19 264:2 268:10 270:1 291:7 293:14 303:5 305:8 306:4 312:17 317:11 333:8 333:20 372:15 384:11,13 419:14 analyze 202:9 302:21 304:13 analyzed 304:16 analyzing 152:4 312:7 Anderson 48:11 48:12,13,16,17 48:18 156:2 444:21 and/or 167:5 182:9 372:8 404:17 anecdotal 412:5 animal 14:14 106:8 179:12 182:1 192:16 268:15 409:21 410:7,11,18,21 411:1 animals 175:19 178:9,14,22 180:5 184:5 193:10 410:2,8 410:12,17 411:2 Anna 8:13 annual 297:23 answer 11:2 15:2 24:13 26:5,23 32:1	38:24 39:3,5 58:16 61:17 77:1,16 83:18 85:14 86:6,9 86:15,16,23,24 88:24 89:3,8 89:10 106:1 115:13 120:22 123:10 138:1,2 144:4 147:24 149:16 156:18 161:17 163:9 178:7 184:12 202:10 203:1,4 203:14 208:10 208:15 231:3 231:19 233:8 245:13 247:3 255:22 256:9 257:12 262:4 267:8,19 268:1 268:2,22 269:8 269:9,10,12 270:5 289:2 296:14 298:15 299:11,13,14 300:14,24 301:4,6,9,10 323:22 326:2,3 326:15 327:13 334:10 343:20 346:7 368:2 403:24 439:18 469:2 answered 20:12 26:18 27:13 60:19 76:9 78:8 80:22 81:18 110:6 111:21 134:7 150:24 163:18 165:9 179:15 179:17 184:2 268:21 271:10 295:20 298:5 298:14 299:8	301:2 312:22 313:15 342:1 480:24 answering 60:13 460:23 answers 10:18 24:5,16 486:5 anticipate 210:13 anybody 96:14 405:4 anybody's 172:10 anymore 58:3,7 185:11 Anytime 329:2 anyway 21:23 41:15 139:5 423:24 appear 40:4 81:5 329:18 377:7 450:10 APPEARAN... 5:3 appears 37:2 52:21 68:16 100:20 103:13 113:15 328:4 459:4 APPEL 4:2 apples 162:7 application 14:21 188:20 189:2 190:6,9 192:18 197:4 208:9 332:16 332:20 381:6 385:4 applications 108:17 332:4,4 applied 189:6 193:22 194:4 232:5 336:12 346:10 441:11 441:15 443:9 443:11	apply 15:14 107:7 441:11 441:11 appreciate 84:7 389:6 approach 13:18 278:3 approached 67:1 appropriate 99:20 149:18 300:17 386:21 452:1 approximately 94:15 315:17 316:24 479:14 479:17 April 7:14 234:1 archived 135:13 area 29:6,11 63:13 107:14 133:9 199:8 212:22,23 233:17 274:5 274:11 380:6 441:2,22,24 442:3 443:1 452:6 453:12 476:16 areas 379:21 389:3 476:3,16 Arizona 48:14 48:18,19 49:11 478:22 479:7 arrive 228:1 Arsenic 6:19 8:19 article 7:17 12:17 31:22 33:14 34:3,11 54:13 90:15,22 91:3,10 142:2 142:9 143:12 143:19 146:24 198:16,18 203:7 207:18
---	---	--	---	--

213:22 217:5	133:11,16	374:3,9,13,14	64:14,18,22	251:8 262:16
234:17 253:9	134:5,9,18	374:19,24	65:4 70:9 76:8	262:17,18
262:13 278:11	138:20 139:16	375:21 377:15	78:8 80:22	266:23 267:24
278:11 294:17	141:1,6 142:10	378:15,23	81:18 83:4,6	269:13 271:11
312:10 328:10	142:21 144:1	380:1 400:3,16	84:2,16,18,19	271:12 296:19
350:23 351:3,7	144:16,22	401:6 404:4	85:13 86:21	301:17 313:3,8
351:21 354:1,4	145:8,17 146:6	410:12,22	101:13 109:9	340:20 342:3,4
354:16,20,24	146:18 147:9	411:2 417:9,13	110:5 111:21	344:5 348:17
374:7 385:23	147:16,21	417:20,21	120:18 132:18	349:9 353:12
389:10,24	148:14 149:1,5	418:6,9 421:13	134:7 150:23	362:9 390:12
390:16,17	149:13 150:4,9	421:14,20	163:18 165:9	407:8 412:4,7
391:7,9,13	150:10,14,17	422:8,17,22	179:15 231:20	424:17
392:17,23	150:20 151:3	423:4,8,13	233:6 268:20	asks 34:14
393:3,9 397:10	151:20,24	424:11 425:21	271:10 289:8	401:20
398:8 447:4	152:7,16	426:2,6,10	289:12 291:9	assess 405:6
articles 13:13	153:14,19,24	427:10 428:6	291:13,22	assessed 111:6
17:23 27:21	154:4,9,15,17	428:13,14,22	298:5,14 299:7	458:11
34:1 43:6 69:8	154:22 155:1,7	429:2 430:16	299:8 300:6	assessment 90:7
70:16,17 98:10	155:16,19	431:5,20 438:9	309:8 310:8	90:20 92:15
104:4,11,15	156:5,23	448:5,13,17	313:15 317:7	281:16 364:7
108:14 141:18	157:24 158:3,8	449:3 451:18	318:9 322:9,20	assist 24:5,10
157:11,22	159:3,7 160:14	452:2 455:14	322:24 342:1	assistant 53:11
214:6 278:7,10	160:16,23	455:18 456:12	342:17,24	348:7,9
278:22 279:6	161:9,14,15,21	456:17 457:15	358:14,14	associated
279:23 351:14	161:21 162:5,8	457:19,23	389:9 449:15	176:18 182:8
351:18 357:10	162:11,12,17	458:4,21 459:8	451:17,21	343:3 368:5
374:5 446:24	162:19 163:1,5	459:8,9 463:19	452:10 454:12	400:7 438:5
462:2,8	163:16 164:1,4	464:2,5,15,20	454:19 456:11	456:7
asbestiform	164:9,14 165:4	465:2,2,11	457:22 461:24	association 7:4
115:16 455:3	165:5,14,14,22	466:9 467:10	463:10 469:8	7:16,18 62:24
asbestos 58:2	166:5,8,13,18	471:21,22	479:22 480:21	159:3 233:16
110:20 111:2	168:5,9,12,14	475:19 476:4,8	480:23 481:9	239:24 243:10
111:12,14,19	168:16,22	476:18,21,23	asking 11:4	253:22 258:22
111:24 112:18	169:3,7,15,23	asbestos-related	26:12 27:7,16	274:17 275:4
115:5 116:24	170:5,6 171:2	339:7 344:15	29:2 45:11	276:6 277:8
117:4,6,9,18	171:13 179:1	345:9	52:6,10 55:23	367:23 368:4
118:1,15,22,23	181:7 182:13	ascend 191:14	61:8 80:24	368:13,15,18
118:23 119:3,5	182:16,20	Ashkenazi 356:8	81:11 86:18	368:19 426:1
121:7 122:12	280:18 338:20	Asian 379:23	87:12 89:5	428:21 429:22
123:15 124:12	339:6,12,18	aside 71:6 231:4	96:23 97:4	430:8,19
124:23 125:7	341:20 342:4	296:19 451:16	108:5,6 116:10	associations
125:21 126:7	342:19 343:14	asked 14:10	130:17 136:1	271:3 311:6
127:1,7 128:6	343:23 344:12	20:12 24:3	145:4 157:10	369:9
128:23 129:3	344:22 345:7	26:18 27:13	162:20,21	assume 11:3
130:13,24	346:21 347:16	43:4 45:5,19	168:14 191:18	94:8 148:3
131:2,4,13,18	347:23 372:9	60:19 61:10,18	205:23 250:14	191:22 202:15

263:16 336:16 379:8,24 463:14 assumed 145:18 284:16 315:23 316:4 336:11 455:22 assumes 366:7 420:18 assuming 117:3 117:4 144:9 145:12,23 175:19 319:22 332:11 386:18 390:24 395:18 396:20 397:10 assumption 110:19 146:2 146:11,21 147:5,18 148:10 152:6 152:14 366:9 377:13 395:10 assure 312:4 ASTM 419:5,15 419:20 420:6 Atlanta 46:9,11 47:7 49:4 atomic 326:7 attached 37:22 53:5 486:7 attempted 107:11,24 108:10 150:1,7 161:19 162:1 162:15 168:19 189:4 191:13 218:19 219:3 302:11 328:10 334:7 373:2,5 375:1 attempts 162:23 attention 157:4 224:19 225:1 225:21 250:11 253:8 258:1	274:24 305:13 305:22 311:14 313:13 361:23 attorney 12:1 42:15 43:14,17 485:11,12 attorneys 14:9 42:6 69:22 70:1,6 72:18 81:20 97:14 395:18 Austin 1:14,15 3:13 44:2 author 16:20 90:15 199:19 199:23,24 200:15 220:21 220:22 304:12 386:4 394:24 authored 93:10 390:17 462:3,8 authoring 351:13 authoritative 229:19 authority 30:4,8 32:7 100:14 229:1 270:21 271:8 280:12 281:8 authority's 270:15 authors 250:12 253:13 263:11 307:13 310:18 395:2 450:11 author's 308:8 311:9 available 14:2 80:3 84:23,24 91:3,8 104:11 224:4 234:12 235:3,5 236:12 243:14 244:4 265:13 281:14 281:20 329:20	Avenue 3:3,12 3:17,21 average 316:7 370:5 371:13 aware 28:5 29:21 34:24 43:6 45:9 46:22 56:19 57:20,22 58:18 67:22 81:19 110:9 115:24 116:22 117:19 121:24 122:5 122:10 123:12 123:18,21 124:9,15 129:18,22 162:14,22 163:8,14 165:4 165:10 167:19 167:24 168:17 192:8,12 222:14 226:2 245:19 246:8 247:11 280:11 280:16 281:8 291:14 326:5 328:9 336:5,8 349:23 361:2,8 384:12 388:21 405:4 407:15 407:21 408:2 411:4 412:12 412:15 414:1,2 416:14,17 417:12,17,19 418:4,14 422:4 422:14 423:2,6 432:8,15 433:6 433:11,13,17 433:20 434:11 434:16,18,22 435:2,5,6,23 436:6,23 437:6 438:8,10 440:24 442:23	471:12 472:15 473:14,21 474:13,16,21 475:4 a.m 1:16 9:5 89:18,19,20,22 139:7,8,9,12 <hr/> B B 4:2 69:14,18 69:20 70:3,6 70:13,22 71:1 71:12,19 72:11 77:8 78:4 79:4 79:5,12 81:5 81:15 320:18 483:5 baby 123:22 124:2,11,20,22 125:20 127:1,7 128:1,5,22 129:2,19 130:2 130:13,23 131:1,3,9,14 131:18 133:15 134:5,8,12,17 134:22 136:18 142:15,19,20 143:6 144:2,8 145:7 146:5 147:19 150:3,8 150:15,21 151:9 165:23 170:6,24 171:16 174:24 175:13 176:2 180:8 182:14 182:16,19 183:6 372:2,17 373:3,10,17,24 375:7,23 377:7 420:15 447:17 448:5 458:6 464:6,16,20 465:3,4,9 468:14 474:1	back 38:2 89:21 89:24 94:7 98:2 120:16,20 139:11 155:8 162:2 165:12 169:20 181:6 195:13 208:11 212:7 213:8,15 219:2 225:13 225:16 253:1 263:3,14 279:21 281:22 315:10 324:20 332:9 378:8 388:13 392:8 393:7 403:2 418:22 430:6 440:12 444:5 445:21 452:9 461:20 background 43:2 419:4,19 420:7 backside 334:6 bad 343:11 377:11 422:13 balance 227:8 banned 29:18 407:18 Banner 48:13,13 444:21 based 76:10 108:22 124:10 159:5 191:23 195:12 201:4 201:17 202:15 202:20 203:20 212:8 217:12 229:7 253:23 259:20 281:18 285:20 301:24 303:23 318:5 318:10 327:9 327:14 338:1 347:17 377:13 385:23 400:11
--	--	---	--	---

423:12,14	359:22 382:7	395:20 413:21	bike 195:18	243:13 244:10
426:3 428:13	believe 13:6	421:3,16	436:16	253:23 254:7
428:23 430:17	25:14 28:8	422:21 429:7	billed 41:21	278:8 279:22
455:24	46:12 49:3	455:2 465:9	219:19	281:21 311:6
baseline 298:24	50:8 53:6	469:19 474:10	binder 68:14,24	319:4 320:22
basically 203:15	56:15 58:7,17	believed 155:6	113:3	335:23 399:14
basis 34:6 75:7	59:1,14 95:16	believes 283:13	binders 69:4,13	399:22 400:1
75:11,14 76:3	111:11 112:16	berating 300:16	71:21 483:4,10	400:18,24
76:6 77:23	119:18 125:2	Berge 8:6 247:7	483:17,21	401:14,24
78:5,10,13	127:6 131:1,18	247:12,14,20	biologic 367:24	405:3,11
87:1 88:21	134:8,11	248:2,11 249:1	biostatistician	407:16 409:8
93:9 125:19	136:12 143:16	249:5,17,24	256:1	409:13 415:16
126:5 127:6	147:4,5 148:12	250:9,16 251:2	birth 56:2 65:7	416:6,16
181:22 190:22	151:19,23	251:16 252:11	bit 10:14 24:22	420:24 433:4,8
bathroom	153:13,23	253:6 257:14	25:22 26:12	434:4,13,15
195:17 436:16	154:4,17	258:2 262:2	44:19 344:8,8	435:17 436:12
Beach 2:10	158:12 161:7	264:2,7,17,21	348:12 480:1	437:2,18
beans 435:3	162:4 163:4	265:7,11	Black 7:13	438:17 439:24
bear 370:22	165:17,23	283:10	Blair 6:16 98:21	440:2 471:5
389:5	173:11 176:5,8	Berge's 257:15	98:23 99:1,6	477:7
bears 113:13	179:16 182:13	259:12 261:11	99:10 100:13	body-only
Beasley 2:2	184:2 192:1	best 8:17 30:8	100:17,20	204:18 205:5
39:16 40:1,5	194:21 198:1	32:16 243:2	blocked 195:2	body-use-only
41:21 42:6	221:6 223:4	255:7 300:14	blogged 462:18	206:7,11
43:14 395:22	227:17 228:6,7	340:10 341:4	blood 2:13 192:9	bold 99:15
395:23 396:2,9	228:14 235:7	341:10,23	432:23 433:2,7	bomb 326:7
becoming 43:10	254:15 255:10	354:3 365:2	434:12,14	bombs 326:22
60:10	261:6 278:8	447:3 479:16	435:16,18	borderline
began 31:7	281:17 282:17	485:9	457:3	241:2
49:23 303:7	285:15,19	beyond 126:22	Blount 141:3,5	bottle 151:9
311:24 316:22	293:1 297:18	134:22	142:23	170:15,24
318:11 349:22	312:11 322:23	bias 99:21	Blount's 141:15	171:11 183:6
349:24	338:12 339:5	103:14 254:2,9	141:17 142:8	372:19 374:24
beginning 1:15	339:11,17,18	254:14 255:9	374:6	452:16 453:1
139:11 253:1	340:7 342:3	255:12 284:22	blueprint	bottles 136:19
269:20 311:15	352:8 359:16	302:12 304:3	391:15	171:2,13 191:6
378:8	361:9 363:19	305:11,17	board 278:20	191:7
begins 9:2 100:6	366:2 369:3	306:5,6 310:24	279:4 363:2,3	bottom 332:10
101:8 227:1	371:14,24	311:5,10,15	363:4	394:20
273:12 317:20	372:2,6 373:11	312:5,12,19,24	body 7:18 15:14	bounds 84:9
begun 323:1	375:22 379:16	313:18,18	15:15 18:13	boys 316:12
behalf 395:6	379:19 380:8	314:1 329:4	23:15 32:15	Bradford 286:1
beings 175:14	380:19,21	BIDDLE 3:6	56:21 189:8	286:7,13,17,24
178:2,3,10	381:2,4,7,9	big 255:3	190:10 196:16	287:4,5 288:16
belief 147:14	385:2,11	bigger 113:11	205:20 211:8	333:13,18,22
191:23 348:15	387:22 389:8	biggest 153:9	215:1 220:15	366:17,23

367:4 368:16	40:22 41:2,5	127:11 128:11	202:18 203:8	279:10 280:19
brain 169:5	41:12,18 44:3	128:17 129:6	203:18 204:11	281:6 282:2
BRC1 337:12	44:17,18 50:17	129:11 130:9	204:22 205:9	283:3 284:19
break 11:8	52:12,17 53:1	130:20 131:20	205:18 206:17	285:11,22
65:21 85:7	54:1 55:15	132:3,10,19,20	207:23 208:20	286:20 287:20
88:16 89:14	57:12 58:8	133:12 134:10	210:4,10,14,18	288:18 289:5
139:5,15	59:6 60:12	135:1,16 136:3	211:2,3,14	290:7,19 292:1
203:12 210:11	61:3 62:18	136:16 137:4,8	212:3 213:7,19	294:5,10,15
211:5,16 213:7	63:7 64:6	137:17 138:8	214:4,5,22	296:3,9 297:5
241:20 253:5	65:12,20 66:8	138:18 139:3	215:9,23	298:6 299:1,10
281:7 315:5	66:10,15,23	139:13 140:13	216:10,20	299:16,18,22
378:12	67:8 68:11	140:20 141:13	217:4 218:18	300:1,18 301:5
breaks 11:6	73:9,17 74:1,8	142:5 143:18	219:18 221:4	301:18 302:6
breast 337:18	74:22 75:16	144:13 145:5	222:5,13 223:1	302:16 303:11
355:21,24,24	76:14 77:6,21	146:1 147:17	224:1,12,17,20	303:18 304:8
356:4	78:12 79:8	148:8 149:2,22	224:22 225:6	305:19 306:2
breath 185:19	80:5,8,16 81:1	150:12 151:6	225:11,14,18	306:15 307:12
475:1,8,11,12	81:12,22 82:9	151:18 152:2	225:19 226:17	307:19 308:7
476:5	82:12,17,21,23	153:12 154:12	228:20 229:23	308:18 309:4
breathe 474:17	83:19,22 84:2	156:12,20	230:15,21	309:16 310:17
474:24 476:22	84:17 85:5	157:3,12,18,23	231:5,8,12,16	313:6,22
breathed 432:6	86:7,20 87:20	158:23 159:11	231:23 232:17	314:18 315:2,5
breathing	87:24 88:5,14	159:22 160:7	233:9,20 236:7	315:12 316:6
342:19 344:2	89:11,13,16,23	161:6 162:13	237:4,22	317:9 318:7
briefly 13:22	92:3,6,16 93:1	163:13 164:5	238:19 239:1,5	319:2,11,20,24
brings 27:23	93:2 94:6 95:3	165:1,20	239:10,13	320:9,15
broad 450:16	95:12,17 97:2	166:11 167:15	240:7,10,14	322:12,21
broader 278:9	98:3,20 101:4	168:10 169:10	242:15,21	323:7,16 324:1
Broadway 2:14	101:21 102:6,8	170:11 171:4	243:3 244:1,9	325:5,22 327:1
brought 58:1	102:17 103:3	172:8 173:8,23	244:18 245:4	327:5 328:8,20
68:2,5,7 394:5	103:10 104:1,7	174:12 175:10	245:16 246:3,5	329:5 330:2,23
Brown 2:13,18	104:16 105:16	175:22 177:1	247:6 248:1,16	331:19 332:14
5:7,10,13 9:13	107:9,20 108:7	177:23 178:11	249:21 252:1,9	333:11,19
9:16 11:17	109:1,12,20	179:3,9 180:2	252:17 253:3	334:19 335:3
12:10 13:14	110:15 111:10	180:20 181:21	253:20 255:13	335:13 336:3
17:10 18:11,21	112:1,11 113:8	182:11 183:3	260:6,16,18	336:19 337:5
19:7 20:16	115:7 116:1,11	183:19 184:13	261:9,22	338:17 339:14
22:1,15,24	117:7 118:10	186:13 187:1	264:13,22	340:19 341:1
23:10 24:1,14	119:1,14 120:1	187:13,21	266:10 267:11	341:17 342:7
26:10 27:3,19	120:17,21	189:3,14 190:7	268:7,17 269:3	342:16 343:10
29:3,15 30:12	121:4,17 122:8	191:9,20	269:11,15,17	344:6,19
30:22 31:14	122:15,18	193:14 195:21	270:11 271:5	345:15 346:17
33:6 35:9,15	123:1,5,8,20	196:5,15 197:5	271:16 272:4	348:1 349:6,7
36:14,20 37:19	124:8,17 125:8	197:18 198:8	273:5 274:23	349:17 350:18
38:24 39:13,14	125:16 126:4	198:23 200:13	275:13,18,24	350:22 353:10
39:23 40:9,17	126:12 127:4	201:12 202:1	276:1,12 277:4	353:22 357:8

363:7 364:1,16	C	55:18,21 56:3	203:22 204:4	303:1 304:4,20
365:4,22	C 2:1 3:1 4:1	56:4,6,8,16,23	205:4 208:15	309:10,22,24
366:14 367:1	320:6,8	57:1,6,16,24	208:24 209:15	310:8 311:7
367:12,18	CALCAGNIE	58:10,22,24	212:10 217:15	316:13 317:21
368:11 369:5	2:8	59:3,9,16,17	217:19 219:9	317:23 324:23
369:18 370:15	calculated 109:2	61:6,12,16,23	220:6,9,19	325:8,13,20
372:13,20,23	256:12	62:4 63:1,18	222:7 224:5	326:1,9,9,11
373:1 374:22	calculation	63:22 64:10,13	226:5 229:2,5	326:15,17
376:14 377:3	256:4 257:14	64:16,20,23	229:15 232:23	327:9,21,22
377:10,20	257:16 259:13	65:7 67:3,13	233:17,24	328:5,13
378:10 380:16	261:11	76:7 106:6,20	234:21,23	331:14 336:22
382:4,18 383:1	calculations	107:23 108:10	235:1 237:7,19	337:11,13,14
384:1,22	452:23	108:11 109:4	238:7 241:7,9	337:18,18
385:19 386:22	California 2:10	109:23 110:4	243:10 244:3	338:4,19
387:13 388:3	2:15	110:18 126:23	244:11 245:9	339:20 340:2
389:9 425:7	call 263:20	138:16 153:1	248:20 251:21	342:6,15 343:2
426:13,21	398:5 478:15	153:11,15,22	253:15,23	343:5,7,22
427:17 448:6	478:18 479:21	154:1,7,18,21	254:8,21 257:9	346:11,21,23
449:6 450:20	481:4,7	155:7,13,16	259:3 264:10	347:19,24
452:3,19 453:2	called 9:9 46:2	156:5,23 158:4	265:17 266:17	348:5,16
453:10 454:1	351:14 360:13	158:9 159:4,20	267:5,15 268:5	350:11,24
455:19 456:20	416:19 449:11	160:2,15,18,23	270:13,19,22	351:23 352:9
458:8,23	481:11	163:16,23	271:2,7,13,17	353:18 354:3
459:17 460:1,7	calling 286:18	164:10,21,23	271:19,22	354:21 355:1,7
460:14,18,21	Canada 90:7,21	165:6,19 166:7	272:9,20,21	355:13,21,24
461:1,12,14,23	281:16	166:10,16,19	273:1,6,8,11	356:1,4,5,13
463:6,9 464:3	Canadian 90:20	166:22,24	273:14,22	357:3,12
464:11,23	canal 442:2,18	167:1,12,19	274:4,14,17	359:15,18,23
465:18 466:6	cancer 7:5,17,19	168:13,23	275:1,5 276:4	360:24 361:5,7
466:17 467:3	7:19,22 8:5,8	169:8,12,17	276:7,14 277:5	361:13 362:5
469:7 470:1,16	8:11,15,18	171:7,17	277:9,23 278:4	362:20 363:1
482:15,18	14:1,22,24	174:15,20	278:6 279:1,19	363:11,18,21
483:18,24	15:7 17:8 18:4	175:2,6 176:4	280:2,13,21	364:20 365:16
Brown's 399:12	18:14 19:12,19	176:9,16,20	281:2,10,19	366:5 368:6
building 42:15	19:23 20:1,8	177:6,11,19	282:17 284:11	372:3 375:24
42:18	20:15,19 21:13	178:16 179:6	289:3 290:18	376:4,6,12,19
bulk 133:15	21:18,20 22:6	179:12,19,20	290:23 291:4	376:24 380:9
223:18	23:4,9,15 25:3	179:22 180:1,9	292:9,21	381:16 382:16
bullets 355:14	25:13 26:1,9	180:15,16	294:23 295:3	387:16 389:11
355:15	26:16 27:11,18	181:18 182:6	295:17 296:16	389:14,19
burden 7:9	28:7,24 30:1	183:12,23	296:24 297:14	395:6 397:15
bursa 409:22	32:6,16 42:23	184:5,8 185:11	297:21,24	399:15,24
Buz'Zard's	43:5,7 44:13	188:7,15	298:10,12,17	400:8,13,18,24
220:16	45:7,14 47:18	189:18 190:5	298:19 299:5	401:13,23
byline 351:8	48:3,4,7 54:14	195:5,24	301:14,16	404:21 405:2,7
B12 433:21	54:18,23 55:7	196:10 197:3	302:2,5 303:1	406:19,21

407:6,11,13,14 407:24 410:3,8 410:13,16,19 411:3,9,15 412:1,10,19 413:13 420:23 421:8,9,15,18 421:20 422:2,5 422:18,23 423:5,10,14 426:2 428:13 428:22,22 429:10 430:4 430:11,17,21 437:3,20 438:6 438:19 439:1 439:14 445:2,6 445:7,9,11 447:4 449:11 454:17 456:5,8 456:10 457:16 458:2,7 462:3 462:10,14,21 463:1 464:16 464:22 465:5 465:17,22 466:3,20 467:2 467:7,9,11,19 467:23 469:1 472:4,23 473:3 473:6 480:18 cancers 21:22 21:22 133:9 160:19,19,20 160:20 238:14 240:22 347:9 406:21 cancer's 223:11 267:6 capable 115:15 116:23 401:12 401:22 402:2 405:1 445:9 carbon 7:13 192:6 carcinogen	458:21 carcinogenesis 25:6 154:6 206:13 220:18 385:5 400:2 carcinogenic 6:9 6:21 7:12 8:21 31:10 127:3 150:17 153:21 154:10 164:14 164:15,16,17 164:18 168:6,7 168:8,9 170:8 170:9 171:9,10 221:3 280:18 280:18 281:3,5 282:1 283:13 283:24 284:18 284:21 285:14 286:23 340:12 372:8 373:7 376:5 377:2 385:5,16 401:5 401:7 402:8,8 403:8,8,12,16 404:4,5,6,8,9 404:19 431:24 432:2 434:6,6 434:8 458:13 458:14 459:3 carcinogenicity 168:3 182:10 205:2 206:12 283:21 432:4 carcinogens 387:17 457:20 carcinoma 238:5 care 4:5 12:22 42:22 59:15 131:9 149:6 186:1 187:4 career 408:5 462:7,13,18 case 1:4 10:3,6,9 29:17 43:9	45:21 56:14,19 57:20 95:2 96:16,24 106:1 107:11 108:9 111:18 152:5 157:7 158:2 170:13 191:23 196:18 203:17 207:4 208:1 216:12,18 225:24 234:16 268:9,19 270:2 271:23 303:4 303:13 359:5 360:22 367:9 370:18 388:20 450:19 464:13 468:6 471:15 473:23,23 482:11 cases 1:6 216:18 216:23 217:3 259:2 308:24 357:20 395:7 case-control 7:6 199:1 235:6,20 236:17 247:24 249:18 250:5,8 253:16 254:1,6 254:14,16 255:6 258:23 259:8 275:6 277:16 287:9 287:23 288:4,9 289:8,11,15,19 290:21 291:6,8 291:16 302:3 302:24 304:13 311:16 327:7 327:10 370:11 387:23 Casper 17:9,17 17:22 18:9 19:5 category 283:23 417:1,2	causal 92:15 159:2 233:16 426:1 428:21 causation 107:17 235:4 268:15 287:12 290:2 causative 237:18 271:4 cause 14:1,22,24 15:7 21:13,18 25:7 26:7,16 27:10 61:12 62:3 106:6 109:3,22 153:14,21 154:18 156:5 167:12 168:13 171:6,17 174:24 177:10 178:21 181:24 182:5 183:12 183:16,22 184:4,10 188:15 189:17 208:24 209:15 213:2 217:14 220:6,9,19 298:9 325:8 339:13 343:9 343:22 346:11 372:7 376:3,5 376:18 381:15 385:4 399:23 400:13 402:15 402:16 403:3 404:12 405:6 406:18 407:2,6 407:10,12,16 407:24 408:9 409:17 411:3,6 411:8,13,15 412:10,18 413:13 420:22 421:9,17,20 422:2 438:24	439:14 445:11 456:2,5,7,9 457:16 459:2 464:16 465:17 465:21 466:19 467:6,9,10,19 467:23 caused 22:3 23:4 28:7 154:21 155:7 178:2 179:12 310:24 344:12 410:8 410:12 416:19 causes 20:2 23:8 27:18 55:20 56:15,23 57:5 57:16 58:10,21 61:23 64:9 67:3 76:6 106:20 107:22 108:9,11 110:18 153:24 154:6 158:3,8 160:23 163:16 164:10,21 166:22,24 168:23 178:15 182:6 184:6 188:2 189:16 189:21 220:24 280:13,21 281:10 284:11 297:14 336:22 339:18 346:21 348:5,16 350:12 351:23 352:9 357:3,12 359:14,23 362:5,20 363:20 372:3 375:23 376:6 380:9,20 381:22 384:5 385:14 400:17 400:24 407:24 410:18 421:7
--	--	--	--	---

421:15 437:20 454:17 462:14 462:21 463:1 465:5 466:3 467:1 469:1 causing 22:18 23:14 212:9 214:14 219:14 339:7 342:20 401:9,12,23 402:12 405:2 406:24 445:10 458:1,7 464:22 caveats 267:3,7 268:3 290:16 cavities 411:3 cavity 19:18 22:12 230:3 457:6 CDC 366:3 cell 215:1 219:13 241:2 241:11,18 242:9 381:21 381:24 382:2 382:16,17 479:24 cells 189:6 221:2 380:23 381:8 382:15 385:15 385:15 406:23 certain 66:1,5 107:1,8 175:24 250:21 284:5 398:16 417:12 464:14 473:18 476:17,20 certainly 18:19 21:12 28:16 82:24 83:11 88:16 121:23 128:23 132:23 160:15 188:1 191:6 260:24 343:8,24 353:1 443:5 451:7	certainty 400:12 CERTIFICA... 5:15 485:1 Certified 1:18 485:3,18,18 certify 485:4,7 485:10 486:4 cervical 166:24 167:1 193:6 cervix 193:5 441:3,6 442:3 442:6,18 456:24 cetera 451:11 cgarber@robi... 2:9 challenge 472:22 challenges 255:2 333:6 challenging 29:12,14 255:1 333:4 334:10 chance 103:8 202:13 284:22 369:24 chances 171:12 Chandler 17:9 17:17 change 30:11 98:2 134:3 148:15 172:1 252:17 311:18 311:18 375:3 378:2 380:23 382:2 409:3 461:8 changed 72:9 237:17 379:17 changes 19:15 19:17 219:17 221:1,2 280:6 381:21,21,23 382:13,14 393:9 406:24 407:2 409:23	456:7 486:6 CHANGE/RE... 487:3 changing 172:4 chapters 63:21 charge 358:15 charged 358:5 chart 113:16 114:12,18 116:3,19 117:8 117:24 119:16 121:8 155:6,9 155:10,11,11 383:13,18 charts 263:6 383:21 416:13 check 92:24 122:1 174:1 386:19 checking 122:6 chemical 170:14 185:17 186:11 chemicals 174:23 175:12 175:24 177:7 181:24 290:3 chest 206:4 339:22,24 343:3,6 440:16 children 387:1,7 China 379:15,24 chocolate 435:4 choose 267:19 360:15 chose 251:23 252:7 264:11 264:24 chromium 111:3 164:16 168:7 372:10 400:5 400:16 404:7 431:24 432:8 432:22 433:1,3 433:7 Chromium's 432:17	chronic 20:24 21:4,4,9 22:13 23:3 217:19,23 217:24 218:5,5 218:10,14,21 380:9 381:16 381:20 406:22 407:4,5,8,10 407:12,13 408:24 456:6,8 circumstance 337:22 circumstances 50:23 cite 22:16 23:1,7 25:18 27:16 193:16 224:3 230:7 283:8 469:13 cited 20:5 72:3 74:18 95:10 101:19 140:1 283:2 382:19 414:3 420:12 449:24 cites 143:1 320:23 383:3 468:9 citizen's 228:22 229:11 232:1 329:12 city 474:17 clarification 52:6 clarify 178:20 308:15 clarifying 172:13 class 303:7 304:2 classification 227:14 283:12 classified 276:4 clear 29:4 39:11 40:21 85:12 152:8 216:11	241:18 322:18 324:21 326:22 349:8 377:4 380:7 444:10 clearly 159:4 426:3 428:23 Cleveland 3:22 client 471:12 clinical 28:13 46:3,5,7,22 47:13 360:12 clinician 33:15 clinicians 360:15 close 67:17 244:12 247:9 354:8 356:3 369:10,15,21 coalition 233:24 363:2,11,19 364:4,20 365:17 coauthors 35:17 480:8 cobalt 111:4 164:17 372:10 400:5,16 404:8 431:24 433:20 434:2,7,12 cofactors 200:12 200:14 cohort 99:18 101:13 103:16 159:5 197:16 236:23 237:10 238:3,11 240:20 242:4 242:13 243:5,8 247:14,21 248:12 249:4 249:10,15 255:3,15 256:22 258:18 258:23,24 259:5,9,14 261:14,20
---	--	--	---	---

265:11,14,21	comes 15:13	228:15 348:3	concentrate	conclude 18:15
266:4,13,22	17:16 126:7	company 25:18	138:19	310:18 457:14
275:6 277:17	270:22 274:13	46:2 51:3,5,8	concentrations	concluded
282:4,11	coming 105:6	51:12 53:10	476:4	159:12 227:9
287:11 288:24	124:21 195:6	73:4,12,16	concept 203:19	275:2 280:12
289:20 293:11	379:20 441:1	77:7 79:10,17	250:17	280:20 307:14
383:10,22	commencement	88:20 147:13	concern 17:21	313:23 384:16
423:14 426:4	485:4	352:14 388:22	20:24 21:9	457:18 484:6
428:24	comment 34:15	416:1,1 446:6	23:9,13 25:5	concludes
cohorts 242:10	429:17	compare 190:22	25:13 26:6	233:14 306:23
247:24 248:11	commentary	191:6 223:7	27:1 28:9	316:23 331:8
249:19 261:12	132:16 149:16	251:7	60:11 61:1	484:3
261:24 262:7	172:4	compared	84:7 126:21	concluding
265:9,11,16	comments 392:4	313:19 346:23	131:11 148:22	341:18 346:20
266:22 268:9	392:12,19	367:23 392:12	151:15 153:9	conclusion
268:19 270:2	393:2,7,9,12	comparing	153:10,17	18:13 27:23
324:12 370:17	393:17,18,19	261:17	155:17 167:5	106:19 148:7
colleague 43:8	416:3	compiled 81:16	175:9 181:18	159:17 160:13
385:21 388:5	Commerce 2:4	81:20	181:19 182:23	160:22 214:23
colleagues	commercial	complete 101:8	196:3 254:13	223:11 227:21
185:23 362:1	136:13,13,14	246:24 427:10	281:1 311:16	228:1 285:20
362:24 371:2	commission	completed 96:9	369:7 370:1	306:16 307:22
colon 337:14	486:17	96:11	373:7 406:22	308:9 314:11
Colorado 130:2	committed	completing	459:10	320:18 322:14
column 159:1	121:2	359:4	concerned 20:3	323:23 340:16
253:12 258:5	committee 2:6	complications	60:24 165:16	340:21 341:3
310:21 425:24	2:11,16 280:6	408:13	177:4,22	347:2 365:9
429:8	361:21	component	180:17 183:2	385:7 431:1
combination	common 187:11	165:15 458:4	183:18 246:22	conclusions
164:20 165:17	238:6	461:6 467:21	255:11 354:21	32:19 102:16
166:9,21,22	commonsense	components	369:20 370:6,7	106:12 188:14
169:15 376:17	295:14	127:2 152:22	407:3 464:21	314:14
404:19	communicated	153:3 154:5	concerning	conclusive
combined	477:24 480:16	162:11 166:9	162:10 176:23	233:15
250:13,23	communication	169:22 173:15	178:23 179:1	condom 195:23
251:5	84:20 85:18	173:18 176:22	179:21 217:18	condoms 16:11
combining	communicatio...	177:21 184:10	353:4	16:24 17:8,15
261:2	86:3	290:4 343:22	concerns 16:15	17:21,24 18:5
come 51:7 59:15	community	379:17 465:9	17:7 20:6	18:14 19:13,16
104:10 206:23	46:16 51:20	composition	45:13 67:12,14	20:9 25:9,19
212:7 213:8	52:2,7,15	170:14 371:23	362:9 376:13	196:8 197:8
253:15 283:5	116:13 133:14	452:24 454:7	384:13,14,21	conducted
326:8 327:7	193:12 194:8	comprehensive	384:23 400:2,8	123:13 303:5
358:13 361:20	194:22 195:8,9	427:7	400:10 437:24	confer 473:11
361:21 365:8	221:8,12,20	comprise 74:13	459:1	conference
411:19 477:6	222:4,12	comprised 259:2	concert 33:10	54:21 462:24

conferences 63:17	30:21 32:4 70:20 74:17	223:10 355:8 455:3,12	385:24 432:17 438:9 446:14	165:7 189:16 305:21 372:22
confidence 263:12,20 284:24 369:9 369:21 370:2	105:2 124:18 127:20 130:1,3 130:10,18 197:23 205:10	considers 226:3 consistency 255:8 288:15 288:20 289:21	469:14 482:11 482:21 containing 16:7 455:3,14	456:18 continue 48:23 202:24
confident 369:15	207:10 211:17 221:13 256:21	367:24 370:17 consistent 66:7	contains 101:12 130:24 131:2,4 134:9,18	continued 126:21 332:1
confirm 71:5 263:16 323:6 328:19	257:13 259:12 261:10 265:12 266:12 268:13 270:20 271:6	240:16 241:23 289:16 290:5,6 290:22 368:15 368:18 370:5,9	139:16 142:21 149:1,5 150:10 162:5,5 184:9 374:9 405:8	contribute 406:18
confirmation 288:14	271:21,24 272:19,24	constituents 166:14	466:24 468:8	contributing 68:10 69:2,10 69:23 75:22
confirmed 119:4	282:3 303:4,13 308:8 311:9,20	consult 104:18 104:20,23	contaminate 373:24	76:22 158:13 158:13 400:17 414:22
conflict 394:20 396:17,21	314:2 317:10 323:8,18 324:3 329:3 341:3,21	consultant 395:1 consultants 478:1	contaminated 110:20 111:19 112:18 121:7 124:22 125:21	contributors 395:24
conflicts 395:3	360:22 367:14 367:22 368:12 368:14 396:23	consulting 396:6 consumed 422:6 422:15	128:6 134:5 141:1,6,21 142:10 143:6	control 56:2 65:7 306:6,9 306:10 432:22 433:2
confounded 312:5	458:20 473:18	consumer 144:10,15 145:9,10 146:8 148:2	143:20 144:1 145:8 149:13 150:4 153:14 163:4 339:6,12	controlled 28:13 200:16 306:5
confounders 200:16	consideration 126:20 127:17	contact 156:11 contacted 362:2 362:18	339:17 341:20 342:18 343:14 344:22 345:6 346:15 373:17 375:11	controls 268:10 268:19 270:2 308:23 370:18
confounding 204:9 284:22	considered 16:9 32:18,22 70:19	contain 15:17,22 16:3 17:1 58:2 69:5,13 145:16 147:16 150:9 171:13 378:13 483:21	contaminating 150:14,20 165:23 374:14	controversial 430:12,22
confused 62:16 130:16	87:17 128:4 130:18 138:14 159:24 187:16	contained 66:18 68:3,24 69:14 71:12,18 95:5 98:5 99:10 104:9 114:10 114:11,21 118:12 138:10 142:8 147:20 151:3 152:7,16 352:20 375:6 378:19 383:12	346:15 373:17 375:11 contamination 115:6 151:8 284:17 418:8 449:3 contemporane... 40:13	control 56:2 65:7 306:6,9 306:10 432:22 433:2
confusing 52:11 58:17	227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		contaminating 150:14,20 165:23 374:14	controlled 28:13 200:16 306:5
confusion 393:24	204:16 223:4 227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		contaminating 150:14,20 165:23 374:14	controls 268:10 268:19 270:2 308:23 370:18
Congress 3:12	204:16 223:4 227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		346:15 373:17 375:11 contaminating 150:14,20 165:23 374:14	controversial 430:12,22
conjunction 40:14 176:21 364:12	204:16 223:4 227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		346:15 373:17 375:11 contaminating 150:14,20 165:23 374:14	conversation 44:4,20,23 45:3,4,19 219:24 478:8
connecting 27:6	204:16 223:4 227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		346:15 373:17 375:11 contaminating 150:14,20 165:23 374:14	conversations 82:20 83:10,16
connection 25:18 29:17 30:14 61:16,19 130:11 138:10 154:14 191:21 193:15 225:23 257:19 340:3 349:11,20 358:7 359:11 372:15 386:8	204:16 223:4 227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		346:15 373:17 375:11 contaminating 150:14,20 165:23 374:14	conveyed 37:16 conveying 38:23 convinced 56:21 57:5 60:10 62:3 357:14
consider 13:2 30:3,7,13,16	204:16 223:4 227:20 278:19 280:17 281:2 301:20 305:7 315:3 322:19 340:21 342:8 345:17 347:18 365:5 369:6 397:11 414:5 420:7 450:18 451:8,13 467:10 469:14 470:4,10		346:15 373:17 375:11 contaminating 150:14,20 165:23 374:14	convincing 382:12 copies 71:18 copy 12:14 31:15 37:7 53:2,5 71:15 71:22 91:4

100:14 120:24	243:6,7,10,11	405:23 406:5	119:9,20	451:7
157:8 214:3	249:1,5 250:6	408:6,10,11,13	140:16 161:10	covered 47:7
224:21 238:20	250:23 253:16	408:16,21	162:17 163:3	49:3 463:4
239:6 240:11	256:1 260:10	409:8 410:23	164:9 340:6	covering 46:4
303:20 394:14	260:22,23	413:13 414:1,7	341:6,19	49:7
424:5 426:15	261:3 263:5,7	414:20,24	343:17 345:18	Cramer 197:20
426:17 427:7	264:23 265:9	416:6 417:10	345:23 416:21	198:10 199:7
corn 407:15,23	266:6 267:24	417:22 420:16	417:2 448:14	200:20 202:2
Corporate 2:9	271:19,20	421:21 422:8	449:1 468:10	207:4,7 234:17
correct 28:19	273:8,14,17	422:18 423:15	COUGHLIN	235:9 329:21
31:4 36:1,7	274:2,3,11,18	425:21 426:7	3:15	330:4,9 331:7
38:7 48:16	276:7,11,24	428:9,10,15,19	counsel 2:6,11	Cramer's
49:14 50:2	277:1,23	430:22 431:5,9	2:16,21 3:5,9	197:23 198:16
51:23 53:16,19	280:21 283:14	431:21,22	3:14,18,23 4:5	200:8 207:10
53:21 55:11	283:16,17,22	432:6 433:14	31:6 35:10	207:24
57:16 58:12	284:1,5,12,24	434:19 436:3	36:16 82:20	created 114:18
60:17 61:7	285:1,8,15	439:5,15,24	83:1,10,17	140:4 304:3
62:1 63:14	286:24 288:5	440:5,9,19,20	85:18 86:3	credit 363:9
64:10 67:3,9	288:10 289:21	440:22 441:3,8	87:13,16 88:8	criteria 286:1,3
69:16 90:8,16	290:9 292:11	441:12,13,16	88:18 89:6	286:7,10,13,17
90:17 93:17	292:12,16,17	441:22 442:3,4	90:2,14,23	286:18,24
94:11 96:7	302:13 305:14	442:6,9,10,13	92:3 93:8,13	288:17 333:13
97:7 98:8,24	310:4 311:2	442:20 443:10	95:12 120:23	critical 300:11
99:3 101:15	312:1 316:14	443:13 444:14	132:21 157:9	critique 248:2,8
106:21 109:15	316:20 317:3	445:10 453:9	157:15 224:21	248:15 293:11
112:20 116:20	321:4,19,22	459:24 462:10	231:20 239:5	317:22 324:11
116:24 120:5	324:9,10	462:15,21	299:16 300:18	324:17 371:10
122:2 125:11	331:14,22,23	463:2,15	392:5 426:14	crocidolite
127:18 131:14	332:17 333:22	465:12 468:10	447:20 448:1	118:8
132:14 147:21	334:22 344:15	468:11 470:11	449:4 462:1	cross 369:16
152:12 156:14	345:3 349:12	471:5,24 472:1	463:17 485:11	442:5,24 443:3
158:19 160:2	350:5 352:5	473:12,20	485:12	450:17 457:2
161:1 167:13	354:12,18,21	474:11 475:1	Counselor 269:6	Crowley 111:6
182:20 183:7	355:14,21	475:12 476:19	country 48:8	172:6 174:2
184:20 185:3,4	356:9,14,18	477:1,4,7,22	couple 41:6	179:13
186:20 193:19	357:13 358:12	482:2,23 486:5	239:11 470:18	Crowley's
193:24 194:6	364:4,7 374:9	corrections	480:14	171:21 172:14
194:12 199:20	377:16,22	486:6	course 46:21	172:16,20
203:24 205:5	381:17 388:22	correctly 24:12	73:2 225:23	173:1,4,10,17
214:9 216:14	388:23 389:14	correlated 21:19	230:6 238:12	174:14 176:1
225:12 226:5	391:8,11,19	correlation	371:9 386:5	376:8
226:10 227:15	392:20,24	264:9 265:4	462:7,13,18	culture 380:23
229:16 230:4,5	396:11,14	439:11	474:18	cure 45:15
230:9 232:9,12	398:17 399:9	corresponding	court 1:1 9:6	curiosity 437:16
234:1 235:10	402:15 403:3	394:23	10:17,20 461:2	438:16
240:18 242:1	403:16 405:14	cosmetic 7:8	cover 47:12	current 134:12

265:22 348:2 359:11 currently 449:1 Curriculum 6:13 cut 105:8 CV 52:21 68:9 69:1 425:11 444:9,14 cycle 433:24 434:3 CYNTHIA 2:8 cytokine 381:23	366:11,24 367:21 368:2,5 382:12 387:14 392:23 395:21 401:15 414:22 423:6 451:10 451:13,14 457:9 476:11 date 1:16 9:4 35:21 44:8 53:19 61:21 62:2 65:13 66:17,22 90:13 94:19 200:3 252:16 309:8 310:22 314:21 415:22 485:8 486:12 dated 36:3 52:22 53:6,15 93:10 94:21 95:6 96:17 351:7 485:19 day 11:7 42:24 49:21 170:22 170:23 479:6 486:16 days 11:22 31:21 173:3 185:16 Dead 192:6 dealing 425:20 deals 355:18 dealt 54:21 383:3 449:16 Debra 7:9 decades 188:6 195:1 321:18 481:23 December 279:13 281:16 354:16 356:12 357:1 decided 114:6 360:9 deciding 60:22	decision 30:10 30:11 269:2 285:8 472:14 decisions 73:5 declared 395:2 decrease 330:10 decreased 202:21 203:22 331:2 332:5 deeming 199:15 defer 115:12,17 451:24 452:8 452:22 453:16 453:22 454:6 define 15:11 22:22 116:8 441:19 defined 170:22 definitely 192:16 390:10 426:17 438:1 470:14 definition 15:18 15:20,23 16:5 16:12 199:1 270:15 271:3 271:15 degree 89:1 400:12 deliveries 387:10 demonstrated 112:17 denial 329:12 deny 328:19 deodorizing 15:16 dependent 110:19 368:20 depends 211:21 211:22 DEPONENT 5:16 486:1 deposed 9:21 deposit 454:8,9 deposition 1:12	6:1,5 7:1 8:1 9:3 10:13 11:13,14,15 12:7,8 31:7,12 35:13 36:18 40:15 52:23 66:13 67:19 95:15 100:22 112:21,23 113:6,17,19,22 113:24 114:3 114:22 118:13 121:9 128:15 128:19 139:22 141:2,4 142:23 157:1 172:7 198:21 213:17 213:21 224:15 233:1 238:22 245:1,2 247:16 269:20 272:2,6 294:13 350:20 353:20 354:1 373:12,15 374:10 415:10 418:24 427:22 482:12 484:3,6 deposits 22:10 453:21,22 depth 13:8 dermal 156:10 241:11 describe 12:15 13:21 105:22 105:24 described 13:18 177:5 290:13 334:16 467:16 describes 12:18 describing 218:22 description 6:3 7:3 8:3 12:24 design 250:22 258:19 designed 257:12	266:1 267:8 268:2 despite 282:17 283:7 detail 124:7 details 34:5 35:7 115:23 291:22 detect 237:12 259:6 262:1,7 317:23 detected 258:22 detection 350:12 351:24 determination 29:22 180:22 182:19 183:5 200:7 207:12 251:11 279:24 283:19 284:4 289:7 318:5 374:13,18 423:12 determine 218:16 223:17 304:1 367:11 determined 122:11 123:14 124:10 130:12 274:15 277:6 284:7,9 285:13 333:21 404:3,4 404:6,7,8 419:5,20 determining 263:10 367:10 Detroit 480:2 develop 325:14 325:20 326:9 326:12 410:2 developing 327:21,22 development 19:23 21:19 174:19 175:7 176:19 180:15 327:9 328:13
--	---	---	---	--

430:4,11,21 devoted 52:1,9 52:14 diagnosed 154:20 304:4 304:20 310:7 diagnosis 8:15 351:1 352:16 diagnostic 46:2 Diagnostics 48:22 diagram 457:5 diametrically 228:2,7 dictate 97:10 dictated 97:9 Diego 2:15 difference 70:11 70:14 161:20 162:16,24 168:3 189:5 198:2,3 237:12 248:14 253:5 297:15,20 304:19 305:1 308:16 311:18 313:21 314:8 383:10 differences 295:6 328:5 337:15,19 379:20 different 25:22 26:12 33:1 37:1 38:13,18 59:22 61:2 87:14 96:2 116:4,15,20 146:21 173:15 181:14 200:11 216:22 223:8 229:10 241:6 258:3 275:19 278:2 287:3,6 287:7 288:8 289:8 307:8,11	307:18 311:8 325:12,13 333:13 337:9 337:11,20,22 337:23 342:13 365:9 379:10 379:20 380:12 389:3 400:14 455:8 differentiate 163:11 differently 197:9 248:9 337:20 difficult 109:8 334:22 335:2,5 335:16 410:17 Dioxide 7:13 Diplomate 1:17 485:3,17 direct 101:6 157:4 198:14 225:20 226:18 226:24 239:2 240:1 253:7 258:1 302:17 303:19 320:17 directed 33:3 directing 224:19 224:24 226:20 274:24 direction 206:24 directly 20:1 406:11 disagree 88:12 234:3 277:22 disagrees 483:17 disclose 50:9 386:2,6,15,17 389:12,17,23 390:2,2,14 391:2 disclosed 391:2 395:12 397:9 disclosure 389:20 395:4	396:17 397:11 disconnect 61:14 discount 314:11 314:19 discover 86:5 discoverable 84:6,14 85:16 87:2,9,22 88:10 discovery 84:21 discuss 83:9 300:21 discussed 105:23 140:23 165:3 471:2 482:22 discussing 139:15 213:23 253:5 294:18 358:2 378:12 discussion 82:13 87:11 202:11 242:19 246:17 258:9,12 262:3 472:9 480:21 481:17 discussions 85:2 87:13,15 disease 188:22 254:20 255:7 267:7 295:5 344:11,15 diseases 186:19 339:8 345:9 disk 139:11 253:1 378:8 dispute 323:6 354:11,15 disputing 354:13 dissolution 51:12 dissolved 22:13 51:10 distinction	160:9 distinguish 234:7 235:7,23 279:18 distinguishing 115:16 116:24 distracted 250:15 DISTRICT 1:1 1:1 DNA 219:15 380:20 407:2 Docket 1:7 doctor 8:17 17:11 18:22 19:9 20:10,18 21:11 22:2 24:2,21 31:5 31:17 33:15,20 35:18 40:7 41:7 47:11 52:18 54:12 55:2 59:20 66:11 67:18 69:18 92:4 97:5 99:15 101:6 102:1,9 102:13 103:5 103:15 104:2 105:18 112:9 112:12 113:4 117:9,16 119:8 123:10 132:12 132:24 134:4 135:10,19 149:24 154:14 160:9 182:12 185:20 186:15 187:15 198:14 201:14 202:19 202:23 203:9 203:20 204:12 210:16,19 211:6 224:3 225:16 226:19 234:14 238:20	239:16 240:4 241:4 245:6,14 251:10 254:6 258:2 260:7 270:13 272:11 278:19 292:19 294:7,16 295:11 299:9 300:13 301:19 302:17 308:19 317:15 320:17 325:6 326:16 341:19 347:3 350:10,23 351:4 353:2,23 354:3 356:24 360:4 371:21 376:15 378:18 384:2 385:20 386:23 390:15 447:4 460:21 473:6 482:19 doctors 47:8 361:10 364:18 document 1:6 11:18 16:23 17:5,18 18:1,1 18:23 19:4 25:18 38:6,9 39:16 41:20 52:18 71:18 74:12 76:5,11 78:11 79:21 113:3 136:24 141:12,24 144:5 202:17 203:5 208:6 216:2 233:5 247:18 278:20 279:12 393:12 447:19 471:1 documentation 257:4 documented 155:5 documents 12:3
--	--	---	--	--

41:1 65:19	dosing 181:16	198:10,16	97:23 172:24	442:15 444:24
66:2,6 67:20	Dr 9:3,14 11:11	199:7,14 200:8	drafting 70:19	465:1
69:14 71:12,14	18:16 26:21	200:20 202:2	drafts 96:13	early 67:22
72:16,20 73:4	27:6 35:17	207:4,7,10,15	97:8,22	350:12 351:24
73:12,16 74:10	36:22 37:15	207:24 213:20	drain 185:18,18	379:23 382:20
74:13,15,18	38:2 39:12	216:6,12	drains 186:12	451:1 473:3
75:2,6,19	40:1 41:4,19	219:20 220:15	draw 323:23	easier 262:21
76:12,13,16,24	45:24 57:4	220:16,16,20	drew 106:12	461:2
77:8 78:3,15	62:20 64:2	230:12 231:24	dried 435:3	East 1:15
78:19 79:10,19	65:4 80:1,9	234:3 235:4,13	DRINKER 3:6	EASTERN 1:1
80:10,14,20	83:8,13,17	236:15 243:4	drinking 421:14	eBay 136:6,7,14
81:4,5,15,24	84:22 85:22,23	253:4 256:6	422:5,6,16	136:19 137:3
82:2,6 83:6	86:4 88:15	267:20 277:22	Drive 2:9	137:12
84:12 85:14	89:3,12,24	280:11 300:24	dropped 326:7	editor 34:14
86:11,23 87:6	90:2 93:4	301:7,8 315:13	Drug 121:24	effect 190:2
88:20 89:7	98:21,23 99:6	340:4 357:17	124:19 126:16	241:11 255:12
90:5 140:1	99:10 100:13	370:23 376:8	234:8	306:11,24
414:4,10,15,19	100:16,20	378:11 380:6	Duces 6:5	307:21 308:10
446:11,15	102:22 107:16	381:1,4 382:5	due 305:22	314:20
483:5	110:16 112:16	382:11 388:4	313:24 410:22	effective 350:12
doing 20:22 46:3	113:13,20	388:17 391:5	DUFFY 3:15	351:24
46:6 47:10	114:18 118:13	392:4 393:6	duly 9:9 485:5	effort 251:3
50:19 83:14	120:3,4,8,11	394:4,10,24	duration 330:5	312:18
185:14 220:1	121:9,10,19,20	395:5,15	330:7	effusion 186:8
286:6 300:15	122:2,7,11	397:16 398:5	dust 17:24	effusions 185:12
357:6 362:12	123:19 126:15	409:9 418:17	dusted 17:15	185:16
365:2 395:16	127:13 128:18	423:19 425:10	dusting 25:11,24	either 218:9,13
458:18 478:10	129:10,12	432:18 444:8	26:6 27:10,17	239:9 278:15
479:23 481:5,9	131:22 132:6	446:3 452:11	28:4,6 30:24	396:3 446:23
dosage 327:17	135:3,6 136:4	452:13,22,23	191:15	458:12 471:23
367:10	136:18 137:6	453:16,16,18	Dusts 6:20 8:19	electron 133:19
dose 107:6	137:10,11,16	453:19 454:6	D.C 4:4	133:23 419:13
109:19,21	137:20 138:22	454:24 455:11	D6620-00 419:5	451:20
110:11,11,12	139:14,18,22	459:15,21	419:20	electronically
181:9,24 219:4	140:22 141:3,5	460:4 461:11	E	71:14
219:12 220:22	141:15,15,17	461:24 463:11	E 2:1,1 3:1,1 4:1	elements 167:17
324:24 328:1	142:23 146:10	463:12,15,19	4:1,6,6	174:14 177:10
329:7,10,13,18	147:2 149:15	464:5,10 468:6	earlier 66:1 90:3	178:1
329:24 330:4	149:18 156:21	470:23 472:20	172:2 196:4	elevation 371:4
331:21 332:22	167:10 170:13	475:20 478:5	221:5 240:18	eliminated
333:4,7,24	171:21 172:6,9	479:21 480:9	332:22 348:13	439:24 440:1
334:3,9,10	172:14,15,16	480:10,11,14	367:21 380:3	Ellen 6:16 99:1
335:1,5,6,10	172:20 173:1,4	480:21 481:3	385:22 388:21	100:13,16
367:5,8,11	173:10,17	481:16 482:2	399:11 415:8	Ellis 3:20 17:9
doses 219:6	174:2,14 176:1	482:10 484:3	436:15 440:5	17:16 19:2
347:23	178:13 179:13	draft 72:7 96:10		else's 15:15

96:14	98:18 100:10	152:4,23 153:4	426:3 428:11	22:17 23:2
elucidate 295:5	103:9 113:21	153:8 188:10	428:23	58:20 75:15
employ 13:17	126:5 211:22	196:17,24	establishes	77:3 100:6
126:13 234:7	212:2,18,21	197:7,9 203:21	337:7	111:13,23
286:24 312:3	213:5,5 233:7	204:17 205:3	estimate 47:22	115:5 125:4,7
313:11	255:11 268:23	205:11 219:3	97:20 150:1	126:3,14
employed 80:19	278:8 279:22	232:21 254:8	452:15 479:16	137:20 138:9
105:19,24	442:1 462:13	271:18,22	estimated 256:8	138:15 143:5
137:19 228:1	entirely 82:21	272:21 285:3	371:14	145:14 146:17
278:2 287:4,4	entirety 232:20	315:14,23	estimating	147:14 155:12
294:19 297:13	entities 2:21 3:5	322:14 328:22	371:17	160:11 177:15
299:3 446:7	3:9	329:7 338:2,10	et 7:9 8:6,13	177:24 192:13
employee	entitled 38:4	340:5 341:4	451:10	194:8 197:2
485:11,12	82:11,19,24	342:9 345:17	ethically 110:9	211:7 214:24
employment	83:11,15 85:2	366:5 467:24	evaluate 137:20	215:10,11,13
54:4	85:5,8 86:4	468:1,3,9,13	243:14 251:4	215:15 216:13
employs 285:24	225:2 272:8	469:13	273:7 286:19	216:21 217:2,7
367:4	278:23 350:24	epithelial 238:6	286:22 295:6	220:14 221:17
enabled 258:18	354:2	241:9,12 242:8	313:10 370:2	222:21 223:3
encounter 155:2	entries 72:12	303:1 311:7	401:15	223:12,18,21
endeavored 15:2	79:13 140:14	339:20 342:15	evaluated 106:9	226:3 227:9,14
304:1	entry 41:24	380:23 382:15	111:15 152:6	227:21 228:8
endeavors 32:15	70:24 71:3	382:17	200:12,15	228:12 230:7
ended 415:15	121:10	epithelium	206:6 226:13	232:22 233:15
416:5 420:14	environment	430:3,10	254:7 286:4	241:10 253:14
endometrial	417:14 474:14	Epstein 7:15	322:22 327:6	253:21 254:18
48:4 440:7,11	474:22 475:5,8	equal 270:1	340:4 402:6	258:20 260:5
440:18 441:1,5	477:10	equaling 307:2	405:9,10	260:10 265:15
endometrioid	environmental	equally 268:10	evaluates 226:8	266:15 268:13
241:2,15	159:18,23	268:19	evaluating	268:14,15,23
endometriosis	164:1,8	equipment	207:11 243:13	268:24 269:1
228:11 273:17	epi 152:7,11,16	417:22 418:9	244:3,10 251:1	269:21 270:7
356:20 440:5	196:6,9 197:14	equivilate 333:4	264:1 311:11	270:10 273:2
441:8	341:10 369:7	Errata 5:17	315:13,22	273:13 274:1
endpoint 302:20	epidemiologic	486:7 487:1	322:13 324:2	274:16 275:3
302:21	45:10 56:20	errors 98:1	338:18 346:18	276:6,11,15,20
endpoints 257:7	268:14,24	263:19,24	383:22 405:13	276:23 277:7
enhance 184:7	286:12 290:1	especially	405:17	278:3 279:17
enrolled 316:18	437:24 438:2	179:22	evaluation 6:9	281:18,24
317:2 321:3,16	468:22 469:3	ESQUIRE 2:2,3	6:20 7:11 8:20	283:20 284:10
322:2	epidemiological	2:8,13,18 3:2,7	31:10 32:11	285:14 290:6
enrollment	100:5,7 102:7	3:11,16,20 4:2	207:18 333:7	313:17 329:7
321:18	260:5,9	essential 432:9	event 201:13	329:10,13
enter 189:7	epidemiology	433:4,21 458:5	Everybody's	339:23 340:10
entire 36:13	7:20 18:3 94:1	established	337:19	341:23 346:14
56:21 74:12	101:23 109:15	159:4 165:22	evidence 14:3	363:19 366:13

366:16 370:8	exceeds 433:9	69:20 70:3,6	450:7 454:22	453:22 454:7
374:19 378:23	434:14 435:17	70:13,22 71:1	470:22,24	expires 486:17
380:1 382:1,21	Excel 113:16	71:12,18 72:11	471:1,17 483:5	explain 37:15
383:4,13 385:2	excerpt 6:19	74:10,18 77:8	exhibits 6:1 7:1	70:14 137:18
385:17,18	428:7	78:4 79:4,5,12	8:1 262:20	153:4 203:17
402:7 408:1,24	exclude 222:6	81:5 96:17	330:14 425:1	264:2 297:14
412:8 418:2	excluded 246:9	97:5,17 98:6,7	446:4,8 462:2	299:3 366:23
420:18 421:5	249:3	98:14 100:21	482:23	456:14
433:6,14	excludes 252:2	100:22 113:13	exists 117:17	explaining
434:11,19	excuse 23:19	114:2,7,10,21	465:10 466:8	284:20
435:15 436:3,7	77:14 82:7	118:12 119:12	expect 201:4,14	explains 284:22
437:13,23	85:21 102:19	120:15,20,24	202:21 203:20	368:17
438:22 448:13	122:14 132:5	128:15,19	212:13	explanation
450:17 454:15	143:13 149:14	129:5,7,10,15	expedite 258:15	259:10 314:6
456:1 467:14	150:22 157:15	132:8,11	experience	392:23
471:22 475:15	176:12,21	138:10 139:22	185:13 223:19	explanations
evidence-based	214:2 226:18	140:2,5,21	280:1 412:5	314:16
6:7 12:18	236:1,20 260:1	156:22 157:1	experiencing	expose 160:16
13:18 31:22	267:17 283:6	157:17,19	161:8,13	exposed 107:13
33:9,13 106:3	287:16 299:12	158:2 198:15	experiments	108:1 109:11
366:21	320:14 403:17	198:21 211:1	481:5	158:22 161:14
exact 90:13	403:19,21	213:17,21	expert 6:14,16	163:1,2,24
103:2 252:15	413:19 419:22	224:14,15	38:4 44:24	164:8 170:24
409:8 429:8	435:21 443:18	225:17 232:20	49:23 50:4,19	201:22 205:12
exactly 11:23	450:15 468:17	233:1 238:21	57:3 62:12	205:20 206:2,8
33:17 97:3	472:17	238:22 245:1,2	65:15 93:14	208:3 259:3
99:9 220:3	exercising	247:15,16	94:22 95:1,7	327:22 341:11
310:3 342:8	195:18 436:17	272:2,6 294:13	96:19,24 111:5	341:16 347:16
355:17 398:4	exhibit 6:4,7,8	294:17 302:8	112:3,7 116:14	347:22 382:14
408:20 478:12	6:11,12,13,14	319:13 350:19	118:16 125:10	436:21 438:18
examination 5:6	6:16,17,19 7:4	350:20 352:21	125:22 126:15	exposure 155:2
9:12 388:15	7:7,11,14,16	353:20,24	128:5 171:22	155:14,19
407:20 446:1	7:21 8:4,7,10	354:9,15	172:11 174:1,9	156:14 158:19
455:1 461:22	8:14,17,19	357:10 373:13	177:16 207:7	159:3,7,18,19
470:20 482:8	11:12,15 12:7	373:14 374:6	207:11 235:21	161:9,10,13,21
482:17 485:4	12:8,16 13:19	391:4 394:6,11	236:18 349:12	161:22 162:16
examined 9:10	31:8,12 33:2,3	394:17 399:9	349:20 357:16	162:17 163:15
350:7	33:8 34:8 35:1	415:10,15	359:2 383:16	163:16,21
examining	35:12,13,19	416:24 418:23	386:3,13	164:10 168:11
168:21	36:5,18 38:3	420:12,14	389:13,22	168:22 169:4
example 143:1	38:10,13,21	424:2,3,8,16	expertise 199:7	181:3 197:1
262:19 273:10	39:17 40:4	425:19 427:3,5	199:23,24	206:16 217:22
274:10 280:7	41:20 52:21,23	427:11,19,22	228:10 453:9	218:4,4,20
312:10 321:16	53:15,20 66:12	428:3,6 446:5	453:13	219:8 227:2
330:4,9 419:2	66:13,19 67:20	446:5 447:20	experts 34:15	275:4,21 276:5
475:19	68:3 69:14,17	448:11 449:12	94:9 452:1,5	276:24 277:8

277:19 302:23 307:7,10 308:4 325:8 327:8 328:12,24 335:10 337:24 338:4,11,15,21 344:12 345:23 346:20 381:11 423:15 426:2,6 428:14,21 429:1,23 430:9 430:16,18,19 449:21 456:16 exposures 421:20 expressed 457:9 expressions 300:8 extent 357:23 361:16 exterior 192:12 192:22 230:8 232:6 external 195:9 328:7 441:1,21 441:23 442:2 externally 441:12 442:17 443:10,12 eyes 244:12 e-mail 37:21 478:2	195:12 207:15 209:9 219:16 221:12,16 232:4 234:18 246:23 256:21 260:21 263:18 264:14 281:2 282:18 288:19 293:10 299:3 300:6 324:12 326:16 342:9 373:6 381:14 390:13 400:13 410:10 423:11 465:7 470:7 475:23 480:1 factor 270:15 273:24 274:7 274:16 276:5 298:21,22,24 301:20 333:21 356:12 361:7 367:14,22 376:11 387:24 472:11 factors 8:12 167:11 199:11 199:14 271:4 273:8,12 276:10,14,19 276:22 295:5 298:17 337:11 337:16 352:15 354:24 355:3,9 359:17 360:22 446:23 447:1,2 447:5,8,11 472:11 facts 292:19 294:20 296:20 296:22 314:16 314:17 420:18 failure 99:19 103:17 fair 11:3 24:21 29:7 31:3	34:23 35:10 36:6 38:6,21 39:4 40:8,17 41:9 47:13 55:18 61:18 64:21 73:12 77:10 84:1 93:11,12 95:4 96:19 97:15 118:16 121:18 167:12 187:6 236:3 243:20 270:18 286:13 327:2 331:24 335:16 349:6 371:11 fairly 331:6 fall 416:24 fallopian 8:7 193:7 272:8 382:16 440:13 442:12,19 456:24 473:19 falls 417:6 familial 355:2 447:5 familial-related 447:2 familiar 10:12 18:12 115:8 117:16 120:10 121:19 184:14 family 59:5 447:1 far 65:9 167:24 168:1 172:7 196:24 328:16 347:18 379:21 386:15 397:8 fascias 406:24 fashion 478:3 480:17 fast 117:14 faster 149:9 fault 246:4 FDA 29:18,22	30:3,7,9,14 122:6,10 123:12,18,21 124:2,9 127:24 138:11,23 140:22 193:13 221:12 228:17 229:14 230:6 232:1,11,15,20 233:13,21 234:12 236:12 236:16 237:18 329:11 365:7 366:3 369:20 384:15,20 385:7 407:18 447:22 448:11 448:15,22 471:3,9,17,20 FDA's 31:2 127:17,20 128:20,22 129:16,18 137:21 230:1 233:23 235:8 235:24 369:7 384:10 448:2 FDA.gov 6:17 feature 258:16 Federal 84:9 87:2 88:11 299:19 300:19 FedEx 368:17 fee 395:1,15,18 396:6 feel 71:7 129:8 143:13 149:17 202:23 245:12 301:9 399:13 fellowship 133:21 481:14 felt 61:1 77:3 254:16 306:8,9 306:9 358:17 female 436:13 437:15	feminine 16:3 315:15 320:20 fibers 118:23 155:13 448:17 452:16 455:4 455:15 459:9 475:19 476:4,8 476:18,21,23 Fibres 6:19 8:19 fibrosis 215:2 408:9,19 409:3 409:4 fibrosus 338:23 407:23 fibrous 111:2 117:12 118:8,8 118:24 162:5 164:14 168:8 170:2 179:2 284:17 372:9 375:4,6,11,17 375:20 377:14 378:14 379:1,2 379:7 400:3,15 401:5 404:5 407:17 456:17 457:4,15,19 459:7,19,23 460:5,8,16,20 465:10 466:10 466:16,19 467:6,9 field 13:3 366:1 397:14 fifth 3:3 356:7 figure 125:10 final 52:18 97:9 97:23 140:8 173:2 380:5,5 482:15,19 finally 384:2 385:20 386:23 financially 485:13 find 8:17 13:12 14:11,12,13
--	---	---	--	---

33:8 51:14	481:14	188:24 190:4	80:1,13,22	173:20 174:4
112:6 130:22	first 12:6 13:8	243:5,9 255:4	81:8,18 83:2	175:4,16
203:6 211:4,5	13:23 14:16	following 389:1	84:13 86:24	176:13 177:13
228:24 233:14	31:16 37:2	454:14,16	88:21 89:9	178:5,18 179:8
237:8 238:7,9	38:3,10 41:19	follows 9:11	93:9 94:24	179:15 180:11
273:3 277:12	41:24 44:23	follow-up 38:1	95:10,13 96:21	181:5 182:3,22
312:9 329:7	65:13 66:17,22	99:21 237:16	97:19 98:17	183:14 184:1
330:17 331:11	74:24 101:7,12	242:16,22	101:1,17 102:3	186:6,22 187:8
331:21 354:2	159:1 181:7	243:4,18,23	103:7,20	187:19 188:17
373:12 424:22	208:10 212:6	244:14 245:20	104:13 105:14	189:10,20
447:3 460:4	220:21 233:13	246:10 257:3	107:3,16 108:4	191:4,17 193:1
471:20 473:3	234:10 242:12	266:6,7 267:1	108:13 109:6	194:14 196:2
finding 14:2,7	253:11 258:5	267:22,23	109:17 110:23	196:12,20
81:10 116:24	277:18 310:21	289:4 290:14	111:21 115:2	197:12 201:7
117:9 118:15	326:11 328:11	290:14	115:21 116:7	201:20 204:2
124:18 156:4	351:4,5 355:5	Food 121:24	117:2 118:4,18	204:20 205:8
160:24 178:13	355:17 362:10	124:19 126:16	118:22 119:11	205:15 206:10
201:14 206:20	379:15 384:15	234:8	119:22 120:14	207:22 209:24
215:5,8 237:5	first-degree	footnote 383:2,8	121:13 122:4	211:11,19
240:21 241:22	355:18	footnotes 382:20	122:22 123:17	214:17 215:7
241:24 291:9	fit 286:9	foregoing 485:7	124:5,14 125:1	216:16 217:1
311:10 317:14	five 48:2 65:23	486:4	125:13 126:1	218:2,24
324:8 368:18	159:5 278:6,9	foreign 23:15	126:10,18	220:12 222:2,9
419:3,18 420:6	325:1 426:4	211:8 215:1	127:9 128:8	222:17 223:14
448:4	428:24 450:24	436:11,19	130:6,15	224:8 226:16
findings 106:16	465:20	437:1 443:16	131:16,24	228:5 229:21
116:3 130:12	fix 98:2	455:15	133:3 134:7,20	230:11 232:14
137:21,21,22	flat 331:9	forgetting	135:3,15	233:4,19 236:2
138:11 152:23	flaws 384:16	370:24	136:11,21	236:20 237:21
164:7 197:23	flip 426:9 429:4	form 13:5 15:14	137:14 138:13	242:3 243:22
204:17 209:19	floor 334:5	18:7 20:12	138:24 140:11	244:7,16
239:23 255:9	flows 192:9	21:16 22:8,21	140:19 145:1	245:23 247:2
288:20 312:11	FLW 1:5	23:6,19 26:3	145:22 147:2	248:6 249:8
312:18 464:7,8	focus 199:4	26:18 27:13	147:23 148:21	251:18 252:6
464:9	293:19	28:21 29:9	149:19 150:6	252:14 254:7
finds 448:22	focused 59:18	30:6,19 33:5	150:23 151:11	254:11 260:9
fine 299:24	63:2 85:3	35:5 36:9	151:22 152:18	261:5,16 264:5
300:3 394:8	folks 244:3	37:12,23 55:14	154:3 156:8,16	264:19 265:19
fingers 97:6	279:19 304:16	57:8,18 58:14	158:21 159:10	266:20 267:18
finish 79:9 82:15	308:21 309:10	60:8,19 62:15	159:15 160:4	268:12 270:24
83:22,24 85:6	310:6 315:24	63:4 64:5 65:2	161:3,24 163:7	271:10 272:23
102:21 210:10	324:4 341:11	65:17 66:21	163:18 164:12	274:20 275:10
213:9 231:18	345:22 354:20	67:5 73:8,14	165:9,11 166:2	276:9 277:3
243:1 299:17	364:4 365:6	73:21 74:6,20	167:14,18,23	279:9 280:15
403:15	366:3	75:6,10,19	169:1,19	280:23 281:12
finished 102:20	followed 188:6	77:15 78:8,17	170:18 173:6	282:23 284:14

285:6,17	377:18 381:19	465:24 466:13	forth 392:12	404:10,16
286:15 288:12	382:10,24	466:22 467:10	485:9	458:14 465:11
288:23 289:23	383:20 384:19	468:20 469:18	found 111:3,14	466:9
290:11 291:19	385:10 386:11	470:13 474:6	117:3 144:22	free 123:15
295:20 297:3	387:5,20 390:7	474:20 475:3	146:6,18	124:12 129:8
298:4,14	390:19 391:21	475:14,22	148:16 174:10	143:14 202:23
299:16,18	395:9 396:4,13	476:6 477:8,12	198:10,18	245:12 301:9
300:2,20	396:19 397:5	478:2 479:15	200:20 209:2	407:1,1 449:2
301:23 302:15	397:21 398:2	480:17 482:20	209:10,21	frequency
303:8,15 304:7	398:20 399:18	486:6	211:7 212:13	108:16 330:7
305:16,24	400:21 402:4	formal 35:2	214:14 215:16	332:1,16,22
306:14 307:5	402:18,23	format 37:1,14	216:13 238:13	frequent 257:5
307:16,24	403:5 405:16	38:14,16	241:1 249:10	291:23 332:20
308:13 309:3	406:1,7 408:15	formation 411:8	290:9 306:10	frequently
309:14 310:15	408:17,23	formed 58:9,20	307:20 313:20	331:17
312:22 313:14	409:11,19	61:22 66:18	369:8 379:2	Friday 35:21
314:13,23	410:15 411:11	78:11,14,24	381:5 400:4	Fridays 42:18
316:3 317:5	412:3,21 413:1	106:17 149:3	402:7 435:3,7	friend 43:8
318:1,14 322:5	413:8,15,20	149:11 150:13	436:24 448:16	358:14
322:16 323:5	414:14 415:4	150:19 151:16	460:8,16	friendly 42:19
323:12,21	415:18 416:9	268:16 281:13	463:24 464:15	480:3
324:16 325:10	417:4,16,24	348:20 357:2	four 40:3 47:8	friends 42:20
326:19 327:3	418:12,16	372:14 411:17	114:21 235:15	59:5
327:12 328:15	419:11,23	formerly 446:6	282:4,11	front 53:2 68:14
329:1,15	420:4,18 421:2	forming 30:16	448:20 471:8	87:18 120:16
331:16 332:7	421:23 422:10	65:14 95:8	471:13	302:8 348:22
333:10,16	422:20 423:17	107:10 108:8	fourth 102:4	349:2 447:23
334:18,24	428:17 430:24	141:20 152:12	227:1 356:3,7	449:13
335:9,21	431:7,11,17	157:6 170:12	fragrance	full 48:6 119:12
336:15 337:1	432:11 433:16	172:17 181:2	174:11 183:5,8	159:1 214:19
338:8 339:10	434:21 435:9	196:18 205:11	183:22 184:3	310:21 428:5
340:14 341:14	435:22 436:5	208:22 271:23	372:11 377:14	444:11,17
342:1,12,23	437:5,22	303:3,12	379:4,5 400:17	fully 59:1
343:19 345:12	438:21 439:7	345:16 360:21	404:11 406:13	fumes 432:6
346:2 347:21	439:17 441:18	forms 75:14	420:21,22	funding 51:3
349:14 350:15	442:22 445:3	76:3,5 77:23	421:3,6	386:16 481:4
353:7 357:5	448:7 449:7	78:5 406:17	fragrances	funny 136:8
362:22 363:22	450:21 452:4	407:5,7	111:4,7 162:6	further 461:22
364:9,23	452:20 453:3	formulate 57:11	164:19 170:4	470:16,20
365:11 366:7	453:10 454:1,3	62:8	171:16 172:19	482:8,17
366:20 367:7	455:5,19,20	formulated	176:20 177:9	483:19 485:7
367:17 368:8	456:21 457:12	62:10	179:13 180:4,7	485:10
368:24 369:13	458:9,23 459:8	formulating	180:22 181:4	future 8:14
370:13 372:5	459:18 460:2	13:23 14:16	183:11,16	350:24 472:8
374:17 376:2	463:4,6,22	formulation	376:9 378:14	
376:21 377:9	464:19 465:14	379:5	400:6 401:8	G

G 4:6	107:13 109:3	given 26:5 54:16	424:19,23	327:13 337:23
Gallagher 42:14	109:22 153:10	55:5,16 78:1	426:11 437:13	341:16 345:13
43:14,21 44:16	191:2,15	85:10 118:5,13	440:14 443:19	371:1 378:3
44:20 67:1,6	192:17,23	126:20 144:6	445:15 460:14	388:4,9,24
GARBER 2:8	197:3 229:6	181:15 183:17	461:12,14	389:2,4 394:12
Gates 242:16,22	259:3 264:9	189:24 246:11	goes 84:19	394:16 397:17
243:4,9 244:20	302:22 309:19	246:23 255:8	134:13 269:18	399:18 401:24
244:23 245:10	336:17 338:5	267:6 269:7	273:23 332:9,9	402:5 425:3
245:18,20,21	356:13 357:2	290:15 299:14	332:9 440:3,12	430:6 435:11
246:1,9 247:12	441:2,21,23	301:12,14	440:13	436:15 444:1
249:13 265:12	442:2 443:1	311:14 333:6	going 14:5,6	445:17 461:16
265:23 266:7	473:17	334:9,14	20:4 24:19	478:6 484:4
266:12	genotoxic 381:3	361:17 367:21	26:4 39:23	Golkow 4:8
gene 380:22	381:8 382:8	415:5 446:19	65:17,24 76:21	good 9:14,15
381:5,5 382:1	geologist 115:10	447:19 479:16	79:6 82:8 83:9	12:24 13:6
382:1	115:12	482:12 486:5	83:17 85:19	53:12,18
general 13:12	geology 453:21	giving 122:9	86:5 87:3,14	135:17 246:14
15:10 21:9	453:23 454:7	130:23 169:7	87:23 88:17	246:19 293:9
33:12,18 48:2	Georgia 49:11	460:22	89:17 91:6	316:11 326:14
106:5 107:17	Gertig 242:18	gloves 19:16	95:22 115:11	388:17,18
126:23 166:18	242:23 243:5	22:4,11,18	115:22 120:14	GORDON 3:11
187:10 228:15	265:23	23:3,8,13	120:19 129:13	gosh 316:11
232:16 286:16	Gertig's 242:17	24:23 25:3,8	134:2 139:6	Gotcha 258:13
287:22 352:17	gestures 300:8	25:12 26:1,7	141:22 149:8	GOTSHAL 2:18
385:16	getting 51:3	26:15 27:1,10	149:20 152:19	3:2
generally 25:5	125:9 130:16	27:17 28:4,7	157:16 165:10	governmental
32:15 33:10	190:24 298:19	28:18,24 29:19	165:12 169:20	480:17
54:12 56:19	345:9 346:14	29:24 31:1	170:23 172:1	grab 38:1
156:10 167:10	352:18 355:7	407:19,20	181:6,13	grains 435:4
193:11 212:20	369:21	go 11:2 13:9	195:16,19	grams 191:10
232:11 258:22	Ghassam 394:24	14:11 48:16,18	196:14,21	grant 386:16
280:4 317:19	giant 215:1	48:19 65:5	197:13 198:13	granulomas
364:17 383:4	girls 159:18	89:13 101:7	203:9 209:1	23:14 407:17
439:8 473:5	give 26:4 47:4	117:14 139:4	210:8,24	407:22
generated 40:5	75:1 91:19	155:8 162:2	211:20 212:1,6	Gray 360:12
generation	100:13 103:8	165:12 181:6	213:11 215:20	great 19:3 33:7
40:14	114:6 122:21	186:18 208:11	219:2 230:11	greater 49:4
genetic 108:22	129:13 137:6	252:18 260:14	230:22 231:8	167:2 238:13
219:16 221:1,1	169:6 202:13	263:3,14	237:14,24	239:23 281:18
355:16 381:10	236:2 238:20	279:21 281:22	238:7 241:8	473:8
381:17 382:13	240:10 254:22	319:17,18	244:21 252:20	Green 360:14
genetically	270:1 301:9	321:12 325:3	260:17 262:5,8	Griffin 17:9,16
328:3	318:23 325:16	330:20 334:4,4	277:15 279:21	17:22 18:9
genital 8:4 14:21	414:9 426:14	334:5 361:20	283:9 285:18	19:2
14:23 106:20	427:1 444:17	365:19 388:6	299:21 315:6	groins 334:5
106:22 107:1	469:5	399:18 424:15	315:20 326:2	group 159:2

227:9 283:16 341:16 426:1 428:20 429:8 430:15,19 455:12 470:10 groups 258:21 365:1 guess 262:5 396:19 417:24 guessing 325:15 guideline 280:3 gut 169:11 GYN 20:22 48:6 94:3 348:8 360:11,11 361:15 362:24 364:12 453:6 480:3 gynecologic 42:21 59:10,21 60:3 62:23 73:3 74:4 133:8 193:12 194:22 195:8 221:19 222:4 222:12 272:14 286:11 296:21 325:24 341:9 352:18 353:2 397:13 398:15 453:7 480:8 481:13,23 gynecological 186:2 292:8 gynecology 223:20 228:9 228:15	156:21 232:19 388:5 391:13 428:2 473:4 handed 31:6 113:12 116:19 121:7 handing 11:11 100:21 213:20 224:13 225:16 272:5 350:23 353:23 handpicked 414:11 Hang 208:5 happen 44:8 95:20 195:12 346:13 409:13 happened 45:4 123:2 263:17 308:19 happens 188:23 189:1 359:5 409:6 439:9 happy 11:9 39:1 40:15,23 42:18 299:11 300:22 301:1 hard 34:22 71:15,17,22 107:4,7 108:17 110:13 162:7 328:19 333:23 334:8,11 336:1 364:21 367:10 375:9 Harlow 320:23 hazard 160:17 head 200:24 310:11 332:23 332:23 health 8:8 30:4,8 30:15 32:6 46:16 48:13 51:20 52:2,7 52:15 55:10 63:9,13,19	64:1 90:7,20 90:21 227:18 236:23,24 237:1,16 242:12 243:6 245:21 246:10 247:1,13 249:4 252:3 257:7,8 265:14,24 266:13 267:3 270:14,21 271:8 272:9 280:12 281:8 281:16 321:3,9 321:10,12,12 321:16 322:23 323:13 324:3 324:14,18 348:3 353:5,13 364:21 365:3 366:1 hear 89:5 220:2 271:12 heard 269:11 399:1,4,4 481:16 482:1 hearing 342:3 399:8 401:19 460:11 heavy 111:2 156:14 158:18 159:6 161:1,8 161:13,20 162:6,16 164:16 165:6 168:6 170:3 179:2 346:20 347:16,22 372:9 373:3,6 373:9,18,23 375:20 377:14 378:14,23 400:3 401:6 426:5 428:14 429:1 430:17 432:9 465:11	466:9 held 1:14 444:10 Heller 7:9 209:7 210:11,13 213:9,22 216:12 help 53:11 112:12 245:5 277:15 362:1 432:22 433:2 helpful 37:24 45:18 243:24 helps 385:12 Henderson 215:22 216:8 217:5 hereinbefore 485:9 heritage 356:9 heterogeneity 250:11,18 251:4 258:20 259:10 hiding 320:11 hierarchy 382:21 383:13 high 171:12 198:19 199:15 200:8 207:13 239:18 263:10 292:3 293:4 295:13 311:23 368:16,22 371:8,10 375:14 421:14 422:6,7,16 423:14 470:8 higher 245:18 246:8 251:16 260:20 262:11 292:15 297:9 347:5 highest 260:9,13 292:20 294:23 295:17 345:22 345:22	highlighted 426:24 highlighting 483:21 high-quality 199:1 246:2 251:12 Hill 286:1,7,13 286:17,24 287:4,5 288:16 333:13,18,22 366:17,23 367:4 368:16 Hilton 1:14 hint 195:6 326:11 329:24 hired 57:2,9,13 58:11 59:23 60:4 61:24 62:11 436:24 Hiroshima 326:6 Hispanics 8:10 295:2,7 histologic 239:3 239:24 241:6 248:4 histology 247:23 248:11 249:20 250:4 historical 135:21,23 459:22 historically 298:1 history 355:20 355:23 356:4 447:1 hold 57:15 67:2 67:12 116:12 132:19 133:13 134:4 150:9 169:2 210:22 336:20 343:13 357:11 430:5 460:10 465:4
H				
H 4:6 half 42:1 210:9 308:24 478:16 halfway 440:21 hand 12:15 31:15 61:11 93:4 120:20				

465:20 holding 444:16 homework 137:10 Hopkins 112:21 112:24 113:14 113:20 114:3,7 114:22 118:13 121:9 132:1,6 138:10 139:22 140:1,5,21 142:22 374:6 hormonal 356:20 447:11 hormone 273:19 369:2,3 hormones 337:17 hospital 10:3 46:13,20 47:6 hotter 318:21 Houghton 265:23 hour 38:5 42:1 79:6 210:9 358:10 478:17 hours 37:16 38:4,15,16 39:8 41:21 42:18 47:5,6 97:15,21 358:6 house 14:4 71:15 housekeeping 483:3 Houston 48:12 48:17 Hulfish 2:19 human 14:13 106:7 166:23 169:4 175:14 178:1,2,9 385:8 434:3 457:19 humans 6:10,21 7:12 8:21	31:10 169:6 175:20 177:11 193:10,11 hundreds 408:4 411:24 437:1 HURST 2:13 hygiene 315:16 320:20 hypothesis 195:7 hypothetical 465:24 hysterectomy 195:4 I IARC 6:8,20 7:11 8:19 31:8 31:9,18 32:10 32:14 33:11,16 156:4,18 158:1 158:18 159:12 159:24 160:21 164:15 187:16 188:1,13 221:23 222:15 223:4,7 224:23 225:21 226:3,8 226:12 227:4,8 227:17 228:2 280:16,20 281:22 282:3 283:6,12,18,23 284:3,7,9,15 284:20,21 285:12,23 286:22 287:4 315:14 316:23 319:3,10,16 320:22 323:9 323:18 340:7,9 340:17 341:22 346:19 347:18 365:7 423:11 423:18,21 424:10,11,12	425:20 426:1 426:10 428:5 429:19 430:13 430:15 431:2,4 431:20 434:7 454:20 455:12 457:10,14,18 459:4 469:9,15 470:10 476:2 476:12,17 IARC's 32:18 154:14 156:22 165:3 285:3 341:3 431:23 454:24 idea 74:11 114:20 169:15 209:16 229:5 295:15 337:2 416:23 419:8 identical 103:5 identification 11:16 12:9 31:13 35:14 36:19 52:24 66:14 100:23 128:16 157:2 198:22 213:18 224:16 233:2 238:23 245:3 247:17 272:3 294:14 350:21 353:21 427:23 identified 239:18 293:3 295:13 311:22 311:23 417:9 identifies 274:5 361:6 identify 18:23 26:13 68:13 75:17 117:5 236:15 274:10 354:24 425:18 identifying 109:13,18	245:18 246:7 262:10 Imerys 3:14,18 79:13,16,17,19 81:5 388:20,22 405:13 406:10 406:14 414:3 414:10,19 415:9 416:14 471:13,15 immune 108:23 337:20 impact 199:12 200:18 impartial 32:15 implication 21:22 importance 352:16 important 19:22 30:15 74:16,23 77:4 128:3 160:8,13 165:21 170:13 181:1 211:17 243:13 258:16 263:9 304:12 305:13 333:8 333:22 353:3 353:14 367:14 367:22 389:12 389:16 390:4 390:13,21 458:20 480:5 improper 261:2 inaccurate 446:15 inadequate 274:16 276:6 276:11,23 inappropriate 300:9 incidence 292:21 294:22 294:23 296:24 297:24	incident 292:9 include 15:17,19 15:22 90:6 143:4 148:14 199:16 221:14 236:8 244:13 244:20 246:12 246:18,23 247:12 249:13 264:11,17,21 278:16 282:8 282:10,13 356:17 377:21 377:23 450:15 450:16 451:12 466:9 included 146:14 245:8,11,15 247:5 249:5 259:1 280:10 451:7 includes 41:20 116:19 186:2 276:23 331:8 470:9,14 including 16:4 16:11 55:20 183:11 220:14 264:7 281:15 343:3 356:19 372:10 448:3 451:9 inclusion 258:17 incomplete 465:24 inconsistent 275:7 277:17 446:18 incorrect 172:12 270:4 increase 153:11 159:20 160:1,5 160:6 163:22 165:18 166:6,7 166:10,15 167:18 169:17
--	--	--	--	--

174:15 176:8 176:15 179:24 180:8,18,19 181:19 190:4 206:12 237:9 238:5,10,14 240:22 241:1 241:14 242:13 249:11,16,20 250:3 251:21 267:5 268:4 290:17,17,23 293:18 297:20 308:2 330:7 331:13,18 332:3,16,19,19 339:19 422:22 increased 18:4 19:12 57:23 164:23 182:9 195:23 196:9 197:2 200:22 204:10 205:4 208:14 237:6 241:23 242:9 265:8,10,16 266:17 267:14 273:13 274:1 275:5 277:9 282:5 290:9 291:17 293:21 307:6 308:3 317:17 331:4 361:18 422:17 423:5,9 438:5 472:13,24 increases 58:23 64:23 160:14 176:3 181:17 219:8 234:24 241:5 248:19 298:23 376:24 387:15 401:1 404:20 increasing 110:4 independent	174:1 262:12 381:12,13 INDEX 5:1 Indiana 49:7,11 51:6,16 Indianapolis 46:10,17 47:9 49:5 51:17 52:8 indicate 19:22 105:18 140:15 359:13 indicated 56:13 90:3,14 93:13 117:24 indicates 118:15 indication 57:22 281:4 indirectly 238:1 indisputable 228:19 indistinguishable... 419:4,19 individual 107:12 108:19 108:20 151:8 170:15 181:12 181:17 183:6,8 256:24 261:20 263:4 298:22 325:12 327:15 328:5 337:15 337:19 357:20 362:23 374:24 individually 77:18 266:5 individuals 243:18 337:8 337:10 338:3 indoor 476:2,15 induced 209:22 induces 380:22 industrial 140:15 416:20 417:1 industries	416:15 inert 192:2,4 194:17,23 221:10 223:21 437:13,17 442:24 443:3 inevitably 407:10 infer 318:24 inference 219:10 322:17 inferring 322:7 infertility 274:10 inflammation 19:22 20:2,5 20:14,14,18,24 21:1,5,6,10,13 21:17,18 22:3 22:5,14 23:4,8 25:7 26:8,8 27:2 28:2,9 174:18 175:7 176:18 177:10 177:18 178:2 178:14,21 179:5,12 180:14,19 181:19 182:1,5 182:9 183:12 183:17,22 184:4,7,10 192:17 210:21 212:23,24 213:2 216:5 217:18 218:21 219:13,14 220:17,24 372:8 376:10 380:9,19 381:12,13,16 381:20 384:6 385:3,14 400:5 400:7 401:9 406:18,20,22 406:23 407:3,4	407:6,8,10,12 407:14 408:9 408:16,18 409:1 411:7,13 411:17 437:20 445:1,7,10,12 454:13,14,16 456:2,4,6,9 459:3 474:2 inflammatory 22:19,23 153:21 170:10 171:20 174:18 175:1,9,13 176:18 177:4 177:17 179:21 180:5 184:19 185:2,8 188:2 188:7 189:17 189:22 209:22 210:2 211:24 212:9,14 214:14,20 215:12,17 217:8,14,23,24 218:6,9,13 287:12 372:12 376:8 377:2 382:3,14 402:9 403:9 404:11 404:12,17 421:4 458:15 inflated 313:12 inflating 307:15 inflation 311:1 313:24 influence 199:11 inform 36:5 140:24 142:9 158:2 256:19 317:21 362:1 362:19 411:12 information 13:11 14:9,12 27:9 30:21 34:7,17,24	36:15 58:6 59:1 70:18,21 75:18 76:4,15 83:1 84:4,10 85:8 86:10 88:8,19 89:6,9 98:5,12 100:19 112:22 117:23 118:6,11 119:18 126:24 127:23 128:4 128:10 136:2 142:8 143:23 146:3 148:6,7 173:9 190:22 196:22,23 223:16 224:3 236:9 243:15 244:4 248:8 254:23 266:3 272:15,21 273:4,12 285:9 287:6,7 288:15 289:4,13 290:15 295:12 323:4,9,14,18 325:16 328:17 329:19 338:13 352:4,13,20 353:13 361:4 365:13 385:24 390:1,24 391:1 416:7,12 420:19 421:10 437:7 458:24 483:13 informative 385:12 448:23 informing 352:17 informs 19:10 141:5 144:20 468:13 ingestion 421:17 422:1 ingredients 6:17
--	--	---	---	---

174:17 176:8 176:15,17 184:4 467:1 inhalation 156:10 204:8 204:14 205:13 206:16 208:4,9 208:18 209:18 338:5,16 340:11 341:4 341:11 345:2 345:24 346:12 347:17 457:1 474:11 inhale 208:23 209:13 345:8 476:23 477:13 inhaling 206:2 475:10 initially 243:19 456:15 initiate 185:2 Initiative 236:24 237:1 265:24 321:9 324:3,14 324:18 initiator 376:11 injected 190:23 inquire 338:20 338:24 inside 184:18 195:15 409:7 409:13 instance 166:23 277:24 328:2 instilled 411:2 Institute 270:14 270:19 271:2,7 271:13,17 272:20 273:7 273:23 274:5 274:15 275:2 276:4,14 277:6 277:23 278:4,6 279:20 280:3 281:20 282:17	449:12 Institute's 271:22 273:12 279:2 institution 137:22 228:17 348:2 444:11 institutions 59:22 187:4 instruct 83:9,18 86:6,14 87:7 88:2 intake 422:21 intend 360:7 362:7,8 intended 353:16 intention 239:22 intercourse 195:16 436:15 interest 363:5 394:21 395:3 396:17,21 interested 43:10 45:20 67:14 95:24 485:13 interesting 480:5 intermittently 47:3 internal 16:22 17:18 25:17 72:16,19 73:4 73:12,15 74:14 74:17 75:1,6 75:18 76:4,23 77:7 78:14 79:18 81:14,23 82:1,6 83:5 88:20 international 32:5 222:7 223:10 224:5 227:18 interpret 132:13 464:7 interpretation	188:18 265:2 285:3 314:5 328:18 366:17 interpreted 366:23 interpreting 116:2 interrupt 82:16 243:2 367:2 interrupted 82:14 202:12 242:20 interstitial 338:23 interval 369:21 intervals 263:12 263:20 369:15 370:2 interview 306:12 307:1 308:11 309:8 310:23 314:21 interviewed 303:6 304:17 307:8 308:5,21 interviews 55:6 55:17 56:13 63:24 intraabdominal 19:17 intrinsic 327:20 328:6 introduce 359:18 436:18 introduced 43:12 436:13 439:1 invasive 302:24 investigate 194:3 220:5 305:13,18 312:18 339:1 343:1 455:21 investigated 110:1 249:1 438:15	investigating 153:2 339:21 438:16 investigation 51:11 194:11 379:9 investors 51:14 invited 54:20 63:16 invoice 37:2,11 38:9,17 39:7 39:15,20 invoices 6:12 36:17,21 37:3 40:1,6 41:3,9 invoked 259:9 involve 193:21 involved 43:11 45:21 60:22 67:15 390:5,15 395:5 397:14 involvement 357:24 involving 456:13 irritant 111:6 irritants 171:20 irritating 162:7 164:20 170:3,9 372:11 401:9 404:12,17 421:5 458:15 issue 14:20 28:19 48:9 87:10 107:5 254:17 364:3 issued 468:5 issues 30:15 54:22 55:10,17 63:18 165:15 237:10 265:20 353:4 364:21 issuing 94:20 Italian 135:22 379:23 Italy 379:14,14	item 31:5 483:3 items 372:16 376:17 377:6 400:15 401:21 <hr/> J January 1:9 5:2 6:2 7:2 8:2 9:4 12:12 31:11 35:22 37:3 38:5 41:22 44:7 49:19 52:22 53:16,20 479:14 485:19 Jersey 1:1 2:20 3:17 Jewish 356:8 job 461:2 John 112:21,23 113:20 114:3,7 114:22 Johnson 1:2,3 1:17 2:21,21 3:5,5,9,9 9:17 9:17 75:18,18 76:5,5 78:14 78:15 114:23 123:22 144:2,2 144:7,9,9,11 144:12,23,23 145:3,3,11,11 145:12,13,15 145:16,20,20 146:5,8,9,19 146:19 147:7,7 147:11,12,15 147:15,19 148:2,3,3,5,5 148:17,17 149:4,4,11 150:2,2,3,3,8,8 150:15,15,21 151:4,9 171:16 174:24 175:12 180:8 372:2,2 373:24,24
---	---	---	--	--

375:7,7,22,23	jury 456:14	394:2,15	482:4 483:20	193:2 195:22
377:15,21	J&J 72:12,17	395:14 396:8	knew 45:9,12,21	196:8 197:22
420:14,15	74:9,12 75:6	396:15 397:1,6	51:6 58:22	200:1,2,19
447:17,17	76:16 79:21	397:22 398:6	62:5 201:8	202:2,4 205:22
459:21,22	80:10 81:4	398:21 399:21	425:15	206:5,11 207:6
468:14,14	135:9,11,13,21	401:10 402:13	know 10:24 11:8	208:21 210:23
474:1,1 485:3	135:23,24	402:19 403:1	22:9 23:21	211:6 212:16
485:17	146:13,15,22	403:10 404:23	31:16 33:20	220:1 223:15
Johnson's	379:10 447:20	405:18 406:4,9	34:2,5 35:2,7	223:19 239:22
114:24 123:22	448:1	409:5,14 410:1	43:4,19,23,24	241:17 244:19
124:2,11 129:2	J&J's 74:14	410:20 411:14	44:1,1 45:6	247:4 257:17
129:19 130:1	123:14 378:13	412:6,22 413:4	47:2,4 65:4	257:18,24
130:13 142:15	378:18 448:3	413:10,16,23	69:20 76:1,4	262:9 279:23
142:18 143:6	449:4	414:17 415:7	77:1 78:6	282:24 286:5
144:8 145:7		415:20 416:10	82:24 83:12	292:7 296:21
147:19 149:12	K	417:7,18 418:3	85:12 86:21	297:7,23 305:3
150:21 151:4,9	K 1:13 3:16 5:1	418:13,21	88:17 91:2,4	313:4 316:10
171:16 174:24	5:6 6:1 7:1 8:1	419:16 420:1	91:22 94:17	317:1,6 318:4
175:13 180:8	9:8 485:4	420:10,20	98:21 99:4,8	318:16,24
377:16,22	486:12	421:12 422:3	104:22 107:6,8	321:2 322:6
journal 34:18,22	Kang 17:8,16,22	422:12 423:1	108:17,18,20	323:3 324:7,22
106:12,14,14	18:8 19:1,9,10	424:1,9,22	109:10,24	324:24 325:4,7
360:12,13,13	20:5	425:5,16	110:7,8 113:14	325:16 326:4
360:14 386:19	KATHERINE	426:23 427:9	113:16 114:9	326:12,15,20
390:1 397:2,9	3:7	427:14,18	114:11,17	326:21 327:2
398:8,11,13	katherine.mc...	428:1,18	115:3,4,8	334:1,2 337:3
journals 35:3	3:7	429:13,16	119:8 127:24	344:16,17
360:6,10	keep 46:5 60:13	431:3,8,13,18	133:10 135:7	346:16 348:10
398:16 399:4	95:23 165:12	432:16 433:19	136:1,8,14	354:5 358:19
judge 86:8,15	216:1 260:16	435:1,13 436:1	137:11 138:21	363:13 365:14
87:8 299:23	300:15 460:19	436:9 437:8	140:4,7,12,14	365:17,18
300:4 401:19	478:13 480:20	438:7,14 439:3	156:17 161:17	368:2 376:7
420:13 435:14	keeping 53:12	439:12,20	164:1 165:12	377:1,12
456:15	KELLERT 3:2	440:17 441:20	165:22 166:17	378:21 379:3,4
judges 401:20	Kemble 3:17	443:7,19,23	166:18 167:4	380:18 386:14
Judith 1:13 5:1	kept 366:4	444:7 445:8,13	168:1 170:14	386:15,19,24
5:6 6:1,5,15	kids 387:15	454:13 455:5	174:5,18	389:22 390:4,8
7:1 8:1 9:8	kind 28:15	455:20 457:12	175:18 176:7	390:14,22,23
38:4 485:4	34:13 43:19	461:13 470:18	177:17 180:13	390:24 393:18
486:12	113:15 169:11	470:21 472:18	180:24 181:2,8	395:19 396:6
Judy 8:18 9:3	185:17 186:11	473:10 474:9	181:9 182:24	396:19 397:17
351:2,5 484:3	358:16,16	474:23 475:6	183:9,15,17	397:24 398:10
Julie 373:11,13	Klatt 3:11 5:8	475:17,24	184:9,11,11	398:12 400:6
373:14,21	5:11 388:7,16	476:10 477:9	187:6 188:22	405:8 410:21
374:11 415:9	388:19 390:11	477:15 479:1	190:1,2,11,13	411:21 412:8
420:12	390:20 392:10	479:18 481:2	190:19 191:10	412:23 413:18

416:4 417:24	259:15,18	465:1	100:18	424:21,23
418:1,18,20	261:14 266:5	lawyers 39:15	learning 43:11	425:18 426:18
419:14,21	267:22	49:24 50:5,10	67:15	427:17,18
420:2,8 421:5	lacking 329:13	57:3,14 58:11	leave 123:9	445:15
421:13 423:21	lag 280:4 325:17	59:23 60:4,17	479:5	level 168:22
427:20 432:14	325:17	61:7,18 62:1	leaves 406:14	184:11,12
432:19 433:3	Langer 120:4,8	62:12 67:21,23	leaving 50:24	473:12
433:23 434:2	121:10,20	72:21 75:1	led 23:3 50:24	levels 183:11
435:12,15	122:2,11	78:1,3 80:11	51:12	419:4,19 420:7
436:2 439:18	123:13 130:12	80:15,19 81:3	left 48:15,17,18	421:14 422:6,8
442:15 454:2	Langer's 120:11	81:24 82:5	49:19,20	422:16 433:7
456:17 466:4	122:7 123:19	84:3 85:13	244:22,23	434:12 435:15
467:5,14,17	Langseth 158:14	86:11,22 87:5	246:11 419:12	437:12
468:2 471:15	language 98:14	91:19 93:15	443:21 444:21	LHG 1:5
472:13 475:9	102:13,14,15	94:10 95:24	468:4,24	LIABILITY 1:4
475:18,23	104:3,6,9	96:6 114:6,8	478:24 483:5	license 49:13
476:2,8 479:4	399:20	118:14 121:8	left-hand 253:12	licensed 49:8
480:3,8 481:20	large 113:15	137:5 207:16	LEIGH 2:2	licenses 49:10
knowing 109:19	151:14 177:18	219:20 358:6	leigh.odell@b...	life 474:19
169:7 175:8	185:7 188:9	358:20 362:14	2:3	lifestyle 447:8
459:2	204:24 205:4	386:8 414:12	length 102:24	lifetime 171:11
knowledge	237:11 266:8	414:16 415:3,6	103:1 108:15	473:5,8
20:21 33:23	266:23	436:24	265:22 290:14	ligation 197:24
43:13,15,16,18	larger 69:4	LAWYER'S	lens 338:12	202:22
228:9 235:17	197:15 297:17	5:18 488:1	lesion 326:13	light 110:14
253:24	387:11 414:9	lay 352:17	letter 7:14	116:14 133:8
known 25:6	414:19 426:15	lead 20:3 22:13	230:13,17,18	limit 262:24
115:15 171:19	426:18	25:3 26:1,9	230:23 231:4,7	263:1
173:14 195:1	late 45:15	29:24 90:15	231:9,11,14,20	limitations
195:13 376:4	latency 316:13	119:18 175:1	232:8 233:22	101:19 109:14
401:4,8 404:11	317:20 325:24	177:3,11	233:24 236:13	109:19 266:3
404:18 457:19	326:16,20	183:12 207:1	362:8 389:10	266:23 289:1
458:13 477:16	327:17 328:11	217:15,18	392:1 393:6,15	290:13 291:20
knows 42:20	latest 282:20	218:5 219:15	393:20	328:22 334:14
43:21	laughing 136:7	leading 22:6	letters 72:12	334:15 367:21
Kramer 207:15	law 10:21 43:19	270:20 271:7	let's 38:24 66:11	368:1
Krebs 433:24	83:20,20,21	leads 20:18 23:9	68:12 70:10	limited 99:19
434:3	lawsuit 88:22	145:14 179:5	94:7 95:23	101:14 103:17
	305:12 313:13	183:22 188:7	99:13 139:5	106:24 255:16
L	lawsuits 302:13	212:10 218:20	158:24 198:9	256:22 257:1,2
L 2:8	303:7 304:2,17	223:4 312:10	210:5 213:7	257:3 259:15
lab 220:20	304:18 305:22	376:11 380:19	215:24 252:18	261:14 267:21
lack 99:19	309:9 311:15	381:21 408:18	260:16 276:2	285:14 448:19
101:14 255:16	311:24	408:21	281:7 315:5	limits 369:9
255:19,21	lawyer 24:3	lead-up 231:13	350:19 388:7	line 119:16
256:23 257:1	52:19 125:11	learn 60:21	403:2 424:15	121:16 487:3

488:3	27:22 34:12,21	386:9 389:13	483:20	135:9 141:23
linear 332:16,19	56:18,22 57:10	390:5 395:5	longer 16:24	144:3 156:17
lines 220:14	57:20,21 58:6	397:15,19	17:15 49:12,16	158:24 172:10
223:20 277:18	58:19 59:8,13	446:20	219:12 243:9	175:17,20
382:16,17	59:19 60:10,15	little 10:14	244:3 326:24	196:23 198:2,7
479:24	60:16,20 61:1	24:22 25:22	331:12	198:9 202:14
lining 439:23	61:5,15,20	26:11 37:1	Longo 112:16	203:3 210:5,20
link 237:18	62:5,7,11	44:19 45:9,14	125:14 126:7	211:22 212:18
423:13 428:12	104:24 105:1	58:17 130:16	126:15 128:14	212:19,20
linking 165:5	106:7 109:8	146:21 212:19	129:13 135:6	213:5 215:20
list 36:17 41:16	110:10 155:15	348:12 362:14	140:22 142:22	217:9 219:1,4
68:9 69:1	156:3 158:11	385:22 443:21	373:19,21	223:6,18 224:9
70:12 73:1	158:12 162:15	477:18 480:1	379:2 380:2	240:22 244:21
76:22 79:11,13	162:23 163:8	live 188:22	452:11,13,22	245:13 246:15
84:24 93:20,23	168:20 169:14	190:1	453:16,18	247:5 248:12
116:3 142:12	174:22 175:5	lived 44:1 190:3	459:21 460:4	251:19 252:15
173:12,17	177:3 187:17	318:19	463:11,15	256:16 257:8
174:1,6,14,17	188:19 206:19	LiveNote 485:18	464:10	257:15 268:23
176:1 177:8	208:2 219:1,3	lives 42:14	Longo's 127:13	272:14 273:3
179:13 273:16	219:11 229:2	living 42:21	131:22 135:3	273:10 278:10
273:19,24	229:15 234:8	423:3,7	136:4,18 137:6	279:23 289:19
356:12,15	234:11 235:8	LLP 2:13,18 3:2	137:11,16,20	289:24 291:12
362:4 371:24	243:14 244:11	3:6,11,15,20	138:22 139:18	291:15 293:16
404:2 414:22	255:11 278:9	4:2	172:15 374:7	295:23 297:16
417:5 432:13	279:18,22	lobby 42:17	459:5,15	297:19 298:21
435:10 447:5	280:6 282:20	location 46:14	463:19 464:5	306:1 308:20
467:1	283:1,4 285:21	51:17	long-term	313:2,17 314:3
listed 69:14 70:3	285:24 286:4,9	locations 46:19	243:23 408:13	314:6 319:8,9
70:21 74:10	289:7 337:7	49:2	411:7,22 412:9	329:16 330:8
77:8 78:4	348:20,22	locum 46:3	472:5	330:24 332:1
81:15 175:24	349:11,16,19	Logan 3:8	look 13:9 16:19	333:3 340:16
276:10 355:2	349:22,23	logical 389:5	17:2 18:18	341:10,15
372:17 376:18	350:1 357:7	long 10:13 44:2	19:18 21:2	346:18,22
377:1,6 385:13	361:16,18	128:24 155:3	24:4 28:17,23	370:7,16,19
396:1,2,10	362:11 382:7	181:11 188:22	32:9 35:24	371:6 391:4
405:1 414:22	412:12 456:1	188:24 190:2,3	38:15,16 72:10	401:2,16
436:15 444:14	litigation 1:5 4:8	218:11 255:4	75:23 77:19	404:13 414:18
listen 149:10	45:12 49:24	267:2 291:23	78:18 79:11	415:19 423:18
lists 70:15 75:22	50:5,11 57:4	317:8,23 318:4	99:13,14 101:5	424:16 425:9
75:23 245:7	57:15 58:12	318:6 322:20	101:18,22	425:17 435:10
382:20 450:7	75:8 93:16	324:13 325:20	103:9 105:9	439:8 443:23
literature 13:12	125:11,22	326:8,12	108:15 111:8,9	445:5 473:1
14:4,5,7 20:7	131:22 138:22	327:24 379:4,6	112:4,6 119:6	looked 27:23
20:21 22:17	207:17 235:22	422:7,15	119:11 126:24	31:18 58:19
23:2,7,16	357:21,24	432:13 477:16	127:22 129:14	71:3,6,9 75:12
25:23 26:13	358:22 359:3	478:15 481:12	133:7,11,15	76:17 77:2

137:1 152:11 156:10,13 168:2 196:7 197:7 199:3,9 200:17 210:21 211:23 212:18 212:22 214:12 214:19 215:14 216:5,17 217:10 222:22 223:2,7,8 237:12 238:10 247:21,23 248:13,18 249:14,18 254:17 256:7 276:17 281:14 305:6 306:7 313:2 318:3 336:9 366:12 366:15 369:10 387:23 405:5 423:22 434:23 436:7 439:4 455:1 458:15 468:9 470:3 looking 12:21 14:3,6 18:10 18:13,23 19:1 19:5,14,16 21:8 24:16 51:6 52:13 73:1 78:22 81:10 100:7 101:23 102:6 102:24 106:7 106:10 116:14 117:15 118:19 129:12 136:22 142:3 152:23 153:2,8 161:8 169:3 173:13 199:16 208:7 212:17 218:6 218:12,15,17 220:3 241:9	248:10 261:18 264:6 270:8 294:6 296:4 302:19 303:9 304:23 305:2 319:23 330:21 330:22 338:11 338:14 339:22 343:8 368:9 378:24 380:12 392:13 393:4 394:10 401:17 424:18,24 425:19 427:2 458:19 469:3 472:10 479:23 479:24 looks 36:24 38:18 39:17 258:3 loop 67:17 354:9 losing 344:3 lot 21:3 146:22 185:11,13 293:8 300:23 305:12,21 334:11 344:1 347:7 354:6 363:5,10 389:2 lots 43:2 399:4 439:13 low 259:8 328:4 328:4 lower 8:11 262:24 292:10 295:3 296:24 298:2 369:9 lowest 227:13 292:21 294:22 295:16 383:17 lunch 213:8,23 lung 160:19 184:19,21 344:1 457:5 Luzenac 471:16 lymph 206:21	206:22,23 207:1 209:3 lymphatic 457:3 lymphocytes 406:23 lynch 337:13 <hr/> M M 2:3,18 3:20 macro 406:23 Magnani 158:15 Main 3:21 maintain 71:11 majority 144:8 145:10 146:7 146:12 148:1 253:14 291:16 321:14 440:2 470:9 makeup 108:22 181:13 290:3 making 73:4 256:21 266:5 389:19 407:1 malignant 185:12,15 186:8 management 186:8 MANGES 2:18 3:2 MANSUKHA... 3:11 manuscript 35:11,16,18,20 36:4 236:18 391:5 394:11 Manuscripts 6:11 marathon 11:7 Margaret 2:3 42:2,4,5 477:17 481:8 481:17 margaret.tho... 2:4	mark 3:16 12:4 12:6 31:7 35:12 52:20 66:11 156:22 198:15 211:1 213:9 238:21 239:21 244:24 247:14 294:7 319:16 320:10 350:19 424:13 425:4 427:16 427:17,18 483:17 marked 6:3 7:3 8:3 11:12,15 12:8 31:12,16 35:13,19 36:4 36:18 52:23 66:13,19 67:19 67:20 96:16 97:5,17 100:22 101:2 128:15 141:11 157:1 157:18 158:1 198:21 213:17 213:21 224:14 224:15 232:19 233:1 238:22 245:2 247:16 269:19 272:2,6 294:13,16 302:8 319:12 330:18 350:20 353:20,24 392:6 394:5,11 425:6,8 427:3 427:22 428:2 454:21 482:22 markers 338:20 market 28:5,10 144:6 marketed 449:1 MARKETING 1:3 marking 128:18 marks 139:10	252:24 378:7 mass 352:19 material 68:10 69:2,10,24 92:4 192:7 415:23 451:8 materials 68:6 70:2,5 72:3 76:22 83:13 84:21 85:20,24 86:19 87:16 91:12,15,20,23 92:2,8,18,20 93:7 106:11 137:2 158:13 192:2,4 312:14 374:4 414:5 446:14 482:20 matter 39:21 58:4 131:5 150:16 151:2 151:12 168:5 169:24 170:4,7 171:3 298:21 matters 453:23 MCBETH 3:7 McCullough 17:18 18:1 MD 6:15,16 7:9 33:14 48:11,12 48:13,16,17,18 156:2 444:21 MDL 1:7 6:12 13:17 14:20 32:20 65:15 415:10 452:11 mean 21:6 22:23 29:5 37:17 38:16 40:18 51:9 71:13 92:11 97:6,21 102:23 104:5 117:14 130:18 132:23 135:11 137:9 170:2 196:21 200:15
---	---	--	---	---

203:15 206:24	46:3,7 47:13	metals 6:19 8:19	297:12 299:2	226:14 227:6
222:6 269:9	49:9 106:4	111:2 162:6	313:9,11,17	227:22 228:13
298:7 339:1	366:22	164:16 168:6	367:3,4 451:19	228:15 336:16
359:4 373:2	medium 151:14	179:2 372:9	452:1	387:3
393:23 418:1	meet 42:12 44:9	373:9,18,23	methods 31:24	Mike 388:19
447:15 448:16	67:6 278:21	375:21 377:15	32:3 106:11	424:21 429:12
459:16 472:21	meeting 36:12	378:15,23	115:11 116:4	472:17
meaning 104:10	42:2 279:4	401:6 432:5	116:20,23	miller 341:22
119:8 133:7	364:11	465:11 466:9	132:13 137:2	millers 340:5
261:1	member 360:17	meta-analyses	246:17 312:6,7	341:6 342:5
means 21:7 74:3	360:19	250:10 251:6	312:14 314:4	343:16 345:18
133:6 284:21	members 278:20	251:20 253:7	418:7	456:13
334:20 413:6	279:4	260:8 265:7	Michael 3:11	mind 15:8 20:10
419:18 420:2	membrane	370:20 451:10	111:5	109:21 129:5
474:24	457:2	meta-analysis	Micheal 1:16	168:12 287:3
meant 84:8	Memorial 46:12	7:23 8:5 99:16	23:20 485:3,17	324:21 336:24
239:16 352:21	memory 121:2	197:16 235:2	microscope	360:7 397:3
379:24 459:19	men 318:24	236:5,10 238:2	133:19 218:7	460:22 464:14
478:23	menarche 316:5	238:3 242:10	419:13 451:20	mine 94:4 416:2
measured	316:8	245:9 247:8,14	microscopes	423:8
189:13 219:7	Menstrual 192:9	250:18 251:2,3	133:24	mineral 117:19
mechanism	menstruation	252:11 258:17	microscopist	minerals 115:17
102:5 220:5,8	228:12 440:12	259:1,5,7	116:5,9 133:1	116:16
220:8 226:4	mention 216:4	260:21 261:3,8	133:5,10	Minerals/Luz...
367:24 380:8	mentioned 43:8	264:2,7 265:3	microscopy	471:24
385:5	246:16 302:4	265:8 283:10	116:14,15	miners 340:5
mechanistic	401:22 438:4	283:11 287:10	133:8	341:5,22 342:5
225:2 227:14	451:14	291:11 329:23	mid 316:18	343:16 345:18
451:10	mesothelial	383:11,23	middle 318:18	456:13
media 305:22	189:6	470:8	321:3 358:18	mines 130:3
311:14 313:13	mesothelioma	method 105:18	middle-age	135:22 343:24
462:19	186:20 187:5	115:9,15 312:3	316:19	379:10 423:4,8
medical 20:7	338:22 339:8	419:5,9,20	migrate 191:1	minimal 251:22
22:17 23:2	339:13,19,23	420:6,8	191:24 192:2,5	mining 79:17
34:12,18,21	342:10,14,20	methodologies	192:13,22	388:22
35:3 38:4 43:1	343:4,16	418:5	208:16 214:8	Minnesota
73:5 104:24	344:11 345:10	methodology	221:7 228:18	49:17
116:13 133:14	345:24 346:9	13:15 14:16	229:6 230:2,7	minus 167:8
133:21 155:23	346:14,16,24	80:18 81:21	232:6 387:17	minute 23:19
195:7 221:8,11	347:5,12,19,24	105:19,24	migration	236:2 370:23
363:2 400:12	410:22	126:13 137:19	192:19 193:13	389:8 475:9,11
412:8 462:9	met 42:17	146:11 152:4	194:16 201:18	minutes 65:23
473:15	463:14 477:18	223:9 227:24	202:20 204:5	79:7 134:3
medicine 6:7	metal 170:3	234:6 251:15	207:1 221:10	210:14,16
12:19 13:18	373:3,6 400:3	268:8 278:1	221:18 223:12	471:3
31:23 33:9,14	432:9	279:17 294:19	223:21,23	mischaracteri...

76:19	423:21 424:11	multipage 468:5	Narod's 259:20	230:16 231:20
misheard	424:11 425:20	multiple 19:20	371:10	245:7 252:17
296:10	426:10 427:8	21:20 106:15	National 270:13	300:22 303:16
mismarked	427:10 428:6	148:23,23,24	270:19 271:2,6	313:7 319:7,9
225:7	431:5,21	166:20 167:11	271:13,17,21	362:4 378:2
misrepresenting	454:20,21	167:17 182:8	272:19 273:6	386:14 423:18
132:22	455:13,17	184:3 191:7	273:11,22	424:19 426:22
misrepresents	457:10,10	199:9,10,11	274:4,14 275:1	450:4,5
132:17 403:22	469:9,15 476:2	223:20 228:11	276:4,13 277:5	needed 109:3
missing 88:1	476:12,17	290:13 298:16	277:23 278:4,5	168:12 185:19
296:18 332:12	monographs 6:8	343:22 387:10	279:1,19 280:2	325:8 371:17
332:12 343:12	6:20 7:11 8:20	391:14 402:7	281:19 282:16	390:2 464:15
misspoke 67:9	31:9,19 33:11	403:7 437:12	363:1,10,18	needing 259:20
239:16 459:13	Montgomery	442:23 458:12	364:20 365:16	needs 120:22
misstates 35:5	2:5	multiply 358:22	449:11	336:24
57:8 77:12	month 49:7	multistep	nature 328:23	negate 208:14
121:13 122:23	279:24 283:7	387:21	435:24	242:6,14
123:17 130:15	439:23 479:2	multivitamins	NCI 234:22	246:13
135:15 139:1	monthly 190:18	432:18,20	272:15 278:20	negative 261:7
147:2 236:21	278:21 279:5	435:7,11	282:18 283:6	neglected 65:24
366:7 402:4,18	months 332:11	museum 135:13	302:4 365:7	neighbors 42:13
468:20	332:13 479:8	Musser 7:15	366:3 450:11	neither 361:5
MIT 130:2	morning 9:14,15	mutation 337:12	NCI's 272:7	485:11,12
mix 21:4 70:7	52:20 67:22	337:14	NCI-sponsored	Network 51:20
110:24 111:1	90:4 172:2,10	mutations	234:19	52:3,15
mklatt@gord...	Morris 480:10	380:22 381:5	NCRA 485:17	never 34:3
3:12	480:11,14	381:10,17	485:18	133:18 171:18
model 410:18	Morristown	382:1	near 206:22	176:14 177:14
models 182:1	3:17	mystery 350:11	423:8 441:15	185:20 326:10
410:21 411:1	mortality 159:6	351:23	441:19	368:2 386:12
moderate 226:9	426:4	M.D 1:13 5:1,6	nearly 10:2	386:13 387:6
modification	motion 348:21	6:1 7:1 8:1 9:8	59:22	389:21 408:1
306:11,24	Mount 3:17	485:5 486:12	necessarily	431:23 433:9
307:21 308:10	120:8		187:6 192:19	434:15 435:18
314:20	move 19:8,8	N	211:21 229:4	438:2 462:12
moment 122:22	78:2 149:15	N 2:1 3:1 4:1	338:15 354:10	462:17,23
Monday 1:9	203:10 299:11	NAEEM 3:20	389:4 477:6	477:20 482:1
money 51:14	300:22 301:1	naive 59:14	481:20	new 1:1 2:20 3:4
358:20 386:7	moved 318:20	name 9:16 16:19	necessary	3:4,17 51:14
395:22 396:7,7	moving 65:17	42:14 46:13	457:24 483:16	69:9 236:8,15
396:11 398:4	216:1 441:2	51:19 97:12	need 11:8 49:4	288:7
monograph 31:9	msilver@coug...	245:7 351:22	80:5,6 86:7,9	newer 197:15
156:22 157:6	3:16	354:2 388:19	86:12,16 112:5	199:5
157:11 165:4	mucinous	410:6,10,11	121:1 122:19	newest 451:4
187:19 224:23	241:18	names 94:2	122:20 128:24	Newport 2:10
225:22 423:19	mud 119:17	Narod 256:6	198:6 202:14	news 55:3,5

65:10	351:15	452:15 456:11	81:17 82:8	186:21 187:7
nicely 286:9	normal 73:2	457:22 462:8	88:23 94:23	187:18 188:16
nickel 111:3	227:11	numbers 78:21	95:9 96:20	189:9,19 191:3
164:17 168:7	North 318:19	297:19 449:24	97:18 98:16	191:16 192:24
372:10 400:5	Northwest 46:12	450:2	100:24 101:16	196:1,11,19
400:16 404:6	Notary 1:18	numerous 91:11	102:2 103:6,19	197:11 201:6
431:24 435:2,6	9:10 486:19	92:17 172:6	104:12 105:14	201:19 204:1
435:16	notations 483:22	468:9	107:2 108:3,12	204:19 205:7
nine 269:12	note 40:10 91:9	nurse 42:16	109:5,16	205:14 206:9
nodes 206:21,22	253:13	348:7,9	110:22 111:20	207:21 209:23
206:23 207:2	notebooks 68:5	Nurses 236:23	115:1,20 116:6	211:10,18
209:3	noted 159:2	237:16 242:12	117:1 118:3,17	214:16 215:6
Nods 200:24	188:1 258:24	243:6 245:21	119:10,21	216:15,24
310:11	416:2 426:1	246:10,24	120:13 121:12	218:1,23
nonasbestiform	428:20 486:7	247:13 249:4	122:3,21,22	220:11 222:1,8
115:17 117:18	notes 5:18 68:20	252:3 257:7	123:9,16 124:4	222:16 223:13
118:1 225:22	71:24 72:2,5	265:14 266:13	124:13,24	224:7 226:15
284:8,11	443:24 478:13	267:3 321:3,10	125:12,24	228:4 229:20
285:13 340:11	480:20 488:1	321:11,16	126:9,17 127:8	230:10 232:13
341:5 469:10	notice 1:14 6:4	322:22 323:13	128:7 130:5,14	233:3,18 236:1
469:15	11:13 12:3	nutrient 433:4	131:15,23	236:3,19,20
Nongenetic 8:12	65:18 66:3	nutrition 432:9	132:15 133:2	237:20 242:2
nongenital	67:19	432:12	134:6,19	243:21 244:6
302:22	November 36:3	nuts 435:3	135:14 136:10	244:15 245:23
nonhereditary	93:11 94:21	N.W 4:3	136:20 137:13	247:2 248:5
356:16	95:6 96:17		138:12,24	249:7 251:17
nonoccupatio...	351:2,8 352:3	O	140:10,18	252:5,13
163:15,21	352:8	O 4:6	144:24 145:21	254:10 261:4
423:3	NTP 384:7,11	oath 10:19 24:6	147:1,22	261:15 264:4
nonserous	384:24 385:8	obesity 356:20	149:18 150:5	264:18 265:18
238:14 239:24	385:11	object 13:5 18:6	150:22 151:10	266:19 270:23
240:13 241:20	number 6:3 7:3	20:11 21:15	151:21 152:17	272:22 274:19
241:23 242:10	8:3 12:2 47:4	22:7,20 23:5	156:7 158:20	275:9 276:8
nonspecific	55:16,17 59:21	23:18 26:2,17	159:9,14 160:3	277:2 279:8
45:16	63:12,16 67:20	27:12 28:20	161:2 163:6,17	280:14,22
nonstatistically	72:11 79:12,13	29:8 30:5,18	164:11 165:8	281:11 282:22
164:7 165:2	96:2 116:3,19	33:4 35:4 36:8	166:1 167:14	284:13 285:5
324:8	152:11 187:4	55:13 57:7,17	167:22 168:24	285:16 286:14
Non-Hispanic	193:17 199:16	58:13 60:7,18	169:18 170:17	288:11,22
8:11	202:7 238:8	62:14 63:3	172:3 173:5,19	289:22 290:10
non-Hispanic/...	254:23 293:1	64:4 65:1,16	174:3 175:3,15	291:18 295:19
296:13	304:19 310:12	66:20 67:4	176:12 177:12	297:2 301:22
non-talc 436:18	331:20 351:13	73:7,13,20	178:4,17 179:7	302:14 303:14
non-talc-based	355:13 368:16	74:5,19 75:9	179:14 180:10	304:6 305:15
438:17	368:20 427:20	77:11,14 78:16	181:5 182:2	305:23 306:13
nopelvicmass....	448:21 451:17	80:12,21 81:7	183:24 186:5	307:4,23

308:12 309:2	409:10,18	440:10 448:6	324:23 385:3	53:19 54:2
309:13 310:14	410:14 411:10	449:6 450:20	October 49:21	61:21 63:8
312:21 314:12	412:2,20,24	452:3,19 453:2	50:24 51:4,15	66:24 68:12,23
314:23 316:2	413:7,14,19	454:3 455:5,9	479:7,9	69:11,17 70:1
317:4,24 322:4	414:13 415:4	455:19,20	odds 262:24	71:17,21 75:17
322:15 323:5	415:17 416:9	456:20 457:12	263:11,15,19	87:24 89:15
323:11,20	417:3,15,23	458:8 459:17	307:15 311:1	90:10 92:6,16
324:15 325:9	418:11,15	460:1,7 463:7	313:24 355:6,6	92:23 93:1,13
327:11 328:14	419:10,22	474:5,20	368:10 369:14	93:18 94:7,12
329:14 331:15	420:3,17 421:1	475:13,22	offered 107:16	94:20 95:4,22
332:6 333:10	421:22 422:9	476:6 477:8,11	344:20,24	99:5,8,13
333:15 334:23	422:19 423:16	479:15	462:24 464:13	100:4 101:11
335:9,20	428:16 430:23	objections 66:5	offering 128:4	101:22 105:6
336:14 338:7	431:6,10,16	66:7,9 67:23	134:16,21	113:2,9 114:9
339:9 340:13	432:10 434:20	observational	278:18 453:8	117:22 120:10
341:13,24	435:8,21 436:4	253:24	453:12	121:18,23
342:11,22	437:4,21	observed 308:2	offhand 178:8	125:19 127:5
343:18 345:11	438:20 439:6	obtain 289:13	191:12	127:12 131:12
346:1 347:20	439:16 441:17	406:3	office 37:13 39:9	131:21 134:2
349:13 350:14	442:21 445:3	obvious 218:13	40:24 47:5	134:16 135:6
353:6 357:4	460:23 463:3	obviously 350:8	71:15	137:18 140:7
362:21 363:22	463:21 464:18	occasional	official 49:21	143:4 144:20
364:8,22	465:13,23	417:21 418:8	officials 50:19	149:8 154:13
365:10 366:6	466:12,21	Occasionally	off-the-shelf	157:20 196:14
366:19 367:6	468:19 469:17	272:17	471:4	196:14 200:6
367:16 368:7	470:12 475:2	occupational	Oh 53:17 177:6	201:3 203:19
368:23 369:12	objected 300:5	155:19 156:6	187:23 263:6	207:6 209:9
370:12 372:4	objecting 346:4	156:14 158:19	309:18 392:9	210:5,7,15,16
374:16 376:1	objection 76:8	159:7,19	Ohio 3:22	213:10 214:11
376:20 377:8,9	76:18 78:7	160:17 161:1,9	okay 9:19,20	216:3 226:2,7
377:17 381:18	79:24 82:16	161:13,20	10:8,11,15,23	226:12,23
382:9,23	95:13 107:15	162:17 163:2	11:6,9,10,21	227:3 229:24
383:19 384:18	110:5 137:23	165:7 346:19	11:24 12:5	231:12 232:10
385:9 386:10	148:20 154:2	346:20 423:15	15:21 16:2,10	232:18 234:6
387:4,19 390:6	156:15 161:23	426:5 428:14	16:21 17:14	235:16,19
390:18 391:20	182:21 183:13	429:1 430:18	19:3 20:4	246:21 247:11
395:8 396:4,12	194:13 267:18	occupationally	23:11 25:17,21	250:20 252:10
396:18 397:4	268:11,20	158:22 162:8	28:11 34:6,16	255:24 256:3
397:20 398:1	270:3 271:9	occur 166:19	34:23 36:24	258:10 262:22
398:19 399:17	298:4,13 299:7	228:16 255:9	37:9,20,24	269:19 273:16
399:19,19	300:1,5,19	381:10 409:3	38:8,12 39:19	277:20,20
400:20 402:3	303:8 307:16	413:6	39:23 42:7	279:16 281:7
402:17,22	313:14 318:14	occurred 83:16	43:20 44:11	284:7 287:2
403:4,20,20,21	326:19 327:3	occurs 166:20	45:2 46:24	288:3,7 291:3
405:15,24	329:1 334:18	193:13 223:22	48:20 50:3	293:6 297:6
406:6 408:22	337:1 433:15	223:23 228:13	51:19 52:16	298:16 303:19

304:5 307:6	oncology 20:22	107:22 108:8	344:21 345:1	order 231:19
309:21 316:7	48:6 94:3	110:16,18	345:16 348:20	280:1 457:24
316:16 321:2	325:24 360:11	111:17 124:21	357:2,11	458:5
344:9 345:21	360:12 362:24	125:20 126:6	361:20 371:23	ore 119:17,19
347:8 350:2	364:13	127:6 128:5	372:15 373:9	140:15,16
351:7,11,20	ones 39:6 93:19	130:23 131:13	373:16,23	454:8
352:7 353:1	94:1,3 118:20	134:4,17,21	374:8 375:3,6	organization
354:8,14,19	148:4 197:19	138:20 139:15	376:15,22	363:15 389:11
357:23 358:4	400:4 414:21	139:18 140:24	377:5,13 378:1	473:15
364:2 370:22	414:23,24	141:5,21 142:9	378:12,18	organizations
371:21 374:23	447:6	143:24 144:21	381:1 384:4,5	362:19 363:8
375:4 380:5	one-time 188:20	145:7,15 146:4	400:14,22	364:19
389:7 391:4	190:5,9,20	148:11,13,15	451:9 462:14	orient 62:20
394:7 395:23	ongoing 257:11	148:18 149:3	463:1 464:13	240:4 320:17
396:16 427:14	online 34:19,22	149:11 150:10	465:4,8,21	original 6:11
429:6 430:7	Oophorectomy	150:13,19	466:2,18,23	39:24 41:3
441:14 443:22	8:13	151:5,7,16	467:5,8,17,20	329:20
444:13 453:15	open 193:8	152:12 158:2,3	468:14,18	originally 41:17
462:6 463:17	336:17 387:9	158:6,8 165:11	482:21	outdoor 476:3
473:14 477:20	443:15 456:23	165:24 166:13	opinions 29:17	476:16
479:11 481:10	456:24,24	167:20 171:15	30:16 32:19	outliers 106:17
483:15	opening 193:4,5	171:19 174:13	36:3,5 66:18	outline 12:24
old 58:3 236:10	193:7 387:11	174:16,23	75:7 76:3 83:3	outside 165:6
283:2	operate 411:20	176:3 178:12	83:7 88:21	193:9,22 194:4
older 470:15	operated 445:1	178:15 180:7	95:5,8 96:18	194:10,24
omitted 245:20	operations	181:2,22	96:23 107:10	195:7,14,15
once 58:24	28:18	191:22 193:17	154:14 157:7	443:15
94:13 170:22	opined 261:12	196:18 201:5	170:12 172:17	ovarian 7:5,8,18
170:22 189:1	opines 179:13	204:12 205:11	191:22 225:24	7:22 8:5,7,11
189:24 279:23	opining 297:13	206:19 208:22	271:23 303:3	8:14,17 14:1
289:1 348:19	opinion 25:1,4	213:1 214:8	360:21 383:17	14:24 15:7
478:5 482:1	25:24 26:14,14	221:6 223:17	387:1 446:19	17:8 18:4,14
oncologist 42:22	27:7,8 29:23	228:13,14	450:12,18	19:12,19,23
59:10,21 60:3	30:24 56:14	229:7 232:5	453:8,12 457:8	20:1,8,15,19
62:23 73:3	57:11,15 58:9	233:7 234:11	457:24 461:8	21:3,20 42:23
74:4 186:2	58:21 61:2,22	237:17 241:4	482:10	43:5,7 44:12
272:14 286:12	62:8,10 64:9	255:18 256:20	opportunity	45:6,13 47:17
292:8 296:22	65:14 67:2,12	259:19 268:16	31:1 76:2	48:3,7 54:14
341:9 348:8	75:11,14,20	270:10 278:18	122:21 129:9	54:18,22 55:7
352:19 353:2	76:6,10 77:1,4	280:1 281:9,13	446:10	55:18,20 56:3
397:13 398:16	77:23 78:5,10	281:17 284:15	opposed 228:2,7	56:4,6,8,16,23
453:6,7 480:3	78:13 79:1	301:20,24	opposite 201:3	57:1,6,16,23
481:13,23	84:5,13 85:15	303:12 325:23	oral 1:12 6:4	58:10,21,24
oncologists	87:1 88:10	327:7 336:10	421:16 422:1	59:3,9 61:6,12
360:11 361:15	89:9 101:9	336:20 338:2	422:21	61:16,23 62:4
480:8	106:18,24	340:4 343:13	oranges 162:8	63:1,18,22

64:9,13,15,20	265:17 266:17	361:13 362:5	191:2,24 192:3	18:16 20:11
64:23 65:7	267:5,6,15	362:20 363:1	192:5,14,23	21:15 22:7,20
67:3,13 76:7	268:5 271:19	363:10,18,20	193:10,23	23:5,18,23
106:6,20	272:8 273:8,14	364:20 365:16	194:5,11,24	24:8 26:2,17
107:23 108:9	274:17 275:5	366:4 368:6	195:10 204:7	27:12 28:20
108:11 109:4	276:7 277:9	372:3 375:24	204:13 208:24	29:8 30:5,18
109:23 110:4	280:13,21	376:4,6,12,24	209:3,11,14,17	33:4 35:4 36:8
110:18 126:23	281:1,10	380:23 381:8	213:2 214:9	37:10 38:22
138:16 153:1	284:11 289:3	381:16 382:15	221:7 227:11	39:4,7 40:8,10
153:11,15,22	290:17,23	382:15 385:15	230:9 232:7	40:20,23 41:8
153:24 154:18	291:4 292:9,21	387:16 389:11	345:2 387:17	41:14 43:23
154:21 155:6	294:22 295:3	389:14,19	409:22,24	44:15 50:12
155:16 156:5	295:17 296:16	395:6 397:14	411:19 434:8	52:5,16,19
156:23 158:8	296:24 297:14	399:15,23	434:10 440:14	53:22 55:13
159:20 160:1	297:21,24	400:7,13,17,24	440:22 442:12	57:7,17 58:13
160:14,18,23	298:9,12,17,19	401:13,23	442:20 443:2	60:7,18 62:14
163:16,23	299:5 301:14	404:20 405:2,7	457:1,16 472:4	63:3 64:4 65:1
164:10,21,23	301:15 302:2,5	406:18,21	473:8,19	65:16,22 66:20
165:6,19 166:7	302:24 303:1	407:6,11,13,14	474:11 477:14	67:4 68:4 73:7
166:10,16	304:4,20	407:24 410:3,8	ovary 154:7,7	73:13,20 74:5
168:13,23	309:10,22,24	410:13,16,19	159:4 204:5	74:19 75:9
169:17 171:17	310:7 311:7	411:3,8,15	206:22,24	76:8,18 77:11
174:15,20	316:13 317:21	412:1,10,19	209:22 211:22	77:14 78:7,16
175:6 176:4,9	317:23 325:8	413:13 420:23	213:6 215:16	79:2,5,24
176:16,19	325:13 326:1	421:7,9,15,17	218:7 335:19	80:12,21 81:7
177:6,19	326:14,17	421:20 422:2,5	335:23 336:7	81:17 82:7,10
178:15 179:22	327:9,21,22	422:18,23	336:13,18,22	82:15,18 83:8
180:1,9,15,16	328:4,13	423:5,9,13	336:24 339:20	83:21 84:1,15
181:18 182:6	331:13 336:22	428:13 429:10	426:3 428:23	84:18 85:17
184:5,8 185:11	337:13,17	430:3,4,10,11	430:21 432:1,3	86:17 87:10,21
195:5,24 196:9	338:3,19	430:17,21	456:4,7,9,18	88:3,12,23
197:3 203:22	339:20 342:6	437:3,20 438:6	477:1	89:15 92:5,10
205:4 208:15	342:15 343:2,5	438:19,24	overall 52:10	92:23 93:22
208:24 219:9	343:7 346:11	445:2,6 447:4	148:22 160:13	94:23 95:9
220:6,9,19	346:21,22	454:17 456:5,8	248:13 290:21	96:20 97:18
229:2,4,15	347:9,19,24	456:10 457:16	368:9	98:16 100:24
232:22 233:17	348:5,16	458:1,7 462:3	oxidation	101:16 102:2
234:21,23	350:11,24	462:10,14,21	406:24	102:19 103:6
235:1 237:6,19	351:22 352:9	463:1 464:16	oxidative 219:14	103:19 104:5
238:6 241:3,7	353:18 354:3	464:22 465:5	380:20 381:22	104:12 105:14
241:9 244:11	354:21 355:1,7	465:17,21	382:2 384:6	107:2,15 108:3
245:9 248:19	355:12 356:1,5	466:3,20 467:2	385:14	108:12 109:5
251:21 253:15	356:13 357:3	467:7,23 469:1	oxygen 407:1	109:16 110:5
253:23 254:8	357:12 359:14	472:3,23 473:3	Oz 64:2 65:4	110:22 111:20
254:21 257:9	359:17,23	473:5 480:18	O'Dell 2:2 5:9	112:8 115:1,20
259:2 264:10	360:23 361:5,7	ovaries 182:10	5:12 13:5 18:6	116:6 117:1

118:3,17	191:16 192:24	280:22 281:11	357:4 362:21	432:10 433:15
119:10,21	194:13 196:1	282:22 284:13	363:22 364:8	434:20 435:8
120:13,18,23	196:11,19	285:5,16	364:22 365:10	435:21 436:4
121:12 122:3	197:11 198:6	286:14 287:16	366:6,19 367:6	437:4,21
122:14,17,20	200:9 201:6,19	288:11,22	367:16 368:7	438:11,20
123:4,7,9,16	202:13,23	289:22 290:10	368:23 369:12	439:6,16
124:4,13,24	203:13 204:1	291:18 293:23	370:12 372:4	440:10 441:17
125:12,24	204:19 205:7	294:3,9 295:19	372:18,21	442:21 443:22
126:9,17 127:8	205:14 206:9	296:6 297:2	374:16 376:1	445:3,15 446:2
128:7 129:4,8	207:21 209:23	298:4,13 299:7	376:20 377:8	448:9 449:9
130:5,14	210:8,12,15,24	299:12,17,20	377:17 380:14	450:23 452:7
131:15,23	211:10,18	299:24 300:3	381:18 382:9	452:21 453:5
132:5,15 133:2	213:10 214:2	301:2,8,22	382:23 383:19	453:14 454:2,5
134:6,19	214:16 215:6	302:14 303:8	384:18 385:9	455:6,23 457:7
135:14,18	216:6,15,24	303:14 304:6	386:10 387:4	457:13 458:17
136:10,20	218:1,23	305:15,23	387:19 390:6	459:11,20
137:13,23	220:11 222:1,8	306:13 307:4	390:18 391:20	460:3 461:4,10
138:3,12,24	222:16 223:13	307:16,23	392:2 393:23	463:3,21 464:8
140:10,18	224:7 225:4,8	308:12 309:2	395:8 396:4,12	464:18 465:13
143:13,16	226:15 228:4	309:13 310:14	396:18 397:4	465:23 466:12
144:24 145:21	229:20 230:10	312:21 313:14	397:20 398:1	466:21 468:17
147:1,22	230:16,19	314:12,23	398:19 399:17	468:19 469:17
148:20 149:14	231:2,6,10,15	316:2 317:4,24	400:20 402:3	470:12 471:2
150:5,22	231:18 232:13	318:14 319:7	402:17,22	472:17,19
151:10,21	233:3,18 236:1	319:17,19,21	403:4,17,19	474:5,20 475:2
152:17 154:2	236:19 237:20	320:2,6,13	405:15,24	475:13,22
156:7,15 157:8	238:17 240:3	322:4,15 323:5	406:6 408:22	476:6 477:8,11
157:15,20	242:2,24	323:11,20	409:10,18	478:19 479:15
158:20 159:9	243:21 244:6	324:15 325:9	410:14 411:10	480:23 482:6,9
159:14 160:3	244:15 245:12	326:19 327:3	412:2,20,24	482:14
161:2,23 163:6	245:23 247:2	327:11 328:14	413:7,14,19	O'REARDON
163:17 164:11	248:5 249:7	329:1,14	414:13 415:4	2:13
165:8 166:1	251:17 252:5	330:20 331:15	415:17 416:9	
167:14,22	252:13 253:17	332:6 333:10	417:3,15,23	P
168:24 169:18	254:10 260:1	333:15 334:18	418:11,15	P 2:1,1,2 3:1,1
170:17 172:3	260:14 261:4	334:23 335:9	419:10,22	4:1,1,6 307:2
173:5,19 174:3	261:15 264:4	335:20 336:14	420:3,17 421:1	page 17:12,13
175:3,15	264:18 265:18	337:1 338:7	421:22 422:9	25:16 38:3,10
176:12 177:12	266:19 267:17	339:9 340:13	422:19 423:16	38:21 39:17
178:4,17 179:7	268:11,20	340:22 341:13	424:5,14,17	41:13 54:3
179:14 180:10	269:6,13 270:3	341:24 342:11	425:3,9,14	70:12 72:11
181:5 182:2,21	270:23 271:9	342:22 343:18	426:16 427:4	77:8 78:4 79:3
183:13,24	272:22 274:19	344:16 345:11	427:12,15	79:11 80:10
186:5,21 187:7	275:9,15,22	346:1,5 347:20	428:16 429:11	81:15 99:14
187:18 188:16	276:8 277:2	349:1,13	429:15 430:23	100:19 101:5
189:9,19 191:3	279:8 280:14	350:14 353:6	431:6,10,16	102:12 105:17

112:13 117:10	Paoletti 143:1	382:19	442:16 443:8	186:3,7,10,18
129:1 157:5	paper 18:9 19:2	papilloma	457:1,5 474:18	187:5 188:5,8
158:24 193:16	19:6,9,10,14	166:23	475:10 477:4	188:11,21
198:14 200:20	19:24 20:6,9	paragraph 99:9	particular 15:8	190:1,3 228:11
221:17 224:19	27:16,24,24	100:5,6,11	153:19 230:12	272:16 293:8
225:1,4,21	92:14,17	101:8,12,24	279:12 336:5	326:3,7 328:6
226:8,13,21	158:14,15,15	102:4,11	336:23 338:14	346:8 348:15
233:13 239:2,6	163:20 198:2,7	112:14 142:24	367:9 372:18	348:17 349:9
239:9 245:7	198:9 202:14	159:1 161:4	379:5 452:16	350:4 352:21
253:8,10	207:13 210:6	214:19 227:1	453:23 454:8	359:19 407:24
255:15 258:2,4	220:16,16	233:13 253:11	particularly	411:12,19,24
260:5 261:13	235:4,13,21	258:5,11	198:19 243:17	412:11 432:21
262:19,22	239:9 244:22	306:17,22	270:21 293:3	445:5 477:21
270:12 273:11	245:13 247:20	320:18	305:11,21	patient's 155:6
274:9 275:1,11	248:3 256:7	parity 387:23	311:14 338:11	340:1
275:14,17	257:22 258:2,7	part 13:15 14:2	395:17	patient-facing
276:3 279:12	259:20 263:15	18:9 19:23	particulates	361:3
290:21 306:18	265:11 280:8	23:12 47:14	228:18 232:16	PAULA 2:13
310:19 319:13	281:17 282:8	49:22 73:10	parties 485:11	pay 250:10
319:19 320:5	286:7 293:20	78:14 94:2	partner 348:11	paying 37:13
332:2 334:14	293:22 294:2	113:5 133:22	partners 196:8	payment 37:22
351:5 367:20	295:1,24 302:4	136:5 139:17	197:8	39:10
371:3 380:7,11	303:10,20,24	141:14 153:7	parts 105:11	pbrown@hbo...
380:12,13	306:23 308:11	158:6 159:16	178:24	2:14
384:3,4 391:15	311:11 312:8	178:22 186:1	part-time 51:22	PC 2:2
394:17,20	313:10 314:15	203:7 218:15	pasted 105:8	PCP 16:22 17:7
418:23,23	314:15 319:10	230:12 249:22	pathologic 19:15	17:24
425:17,24	322:7,18	258:7 263:16	19:17 445:4	PCPC 17:18
426:10,20	332:18 340:8	277:10 332:8	pathologists	25:15
428:4,12 429:5	360:2 361:24	332:10,10	436:23	PDQ 8:8 278:23
429:17 448:11	368:17 381:4,9	343:12 352:12	pathology 21:2	449:11
449:19 450:6	381:24 382:22	356:24 361:23	133:8 155:12	peas 435:3
455:10 487:3	384:16,21	427:11 433:21	212:19	peer 34:2,8 35:7
488:3	386:9,13 393:7	459:6	patient 12:22,22	391:10,12,15
pages 38:12 40:3	397:16 425:11	particle 7:9	154:21,24	391:19 392:11
114:21 224:4	436:16 438:3	194:3,9 212:13	155:2,14,18	392:16 393:12
275:16 391:14	474:8 480:9	443:16	156:1 185:18	peer-review
486:5	papers 18:8	particles 192:6	325:12 338:19	263:17
paid 207:16	19:20 62:6	192:11,13,21	352:13 407:19	peer-reviewed
358:20 389:18	63:13 163:19	214:8,13 221:6	472:3,10	33:19,21,24
395:15,18,19	169:3 177:20	223:22 230:2	patients 46:24	35:2 54:13
397:18	281:23 287:12	230:24 232:11	47:18,21 48:1	106:13
pancreas 433:1	287:12 312:17	336:17 417:21	48:8,24 52:2	pelvic 206:21,23
panel 34:14	312:24 328:18	436:11,19	52:10,15 59:2	207:1 352:19
panties 333:2	329:9 334:7	437:1,13,17	59:11,14,15	pelvis 440:14
334:4	371:7 380:21	438:17 441:10	60:6 185:12,22	443:2

pending 90:7	320:21 321:15	230:2 335:7,12	478:15,18	357:20
Penninkilampi	322:8 371:4	400:23 406:3	479:21 481:4,7	plaintiffs 2:6,11
235:2 236:5	375:13,14,16	439:2 456:23	physician 46:18	2:16 12:2 24:3
238:2 240:17	375:20 411:19	period 44:10	51:21 73:11	31:6 36:16
240:20 244:19	473:8	47:6,15,18,23	156:1 397:12	43:17 49:24
245:1 246:7,9	percentage	48:11 50:14	physician's	50:4,10 52:19
246:13,19,22	51:24 52:8	115:6 170:23	348:7,9	57:14 58:11
248:9,18 249:3	74:11 121:14	243:20 316:13	Ph.D 481:19	59:23 60:4,16
249:12 250:10	131:3,6 149:4	317:20 325:17	picked 358:16	61:7,17 62:1
251:2,11,15,23	149:6 150:2,8	325:18 326:1	414:10 415:2	62:12 66:4
253:6,8,13	309:11 336:6	326:17,20	picking 81:4	67:21,23 72:18
260:12,19	perfectly 27:5	327:18 328:11	picture 351:4,9	72:21 78:1,3
262:10,13,19	perform 256:3	351:12 362:17	351:21 354:2	80:11,15,19
262:23 263:5	452:14	410:5 473:18	picturing 460:19	81:3,20,24
264:1,8,15	performed	periods 114:14	piece 30:20	82:4 83:6 84:3
265:1 283:10	46:15 115:23	378:20 422:7	36:15 70:20	88:18 90:3,24
329:23 470:7	121:10 185:21	422:15	71:4 138:17	91:19 93:9,15
Penninkilamp...	433:18 435:24	peritoneal 8:7	196:22 212:19	94:10 96:1,6
241:24	448:12	230:3 272:9	248:8 270:6	97:13 112:3,7
Pennsylvania	perineal 7:8,21	410:22	385:17	118:14 125:11
3:8	110:17 161:21	peritoneum	pieces 70:18	125:22 126:15
people 15:14	189:8 191:15	440:9	273:2 385:1	137:5 207:8,16
28:17,23 43:2	192:18 208:9	peroneum	Pier 373:13,21	235:21 236:18
45:20 96:2	209:4,13 227:2	190:17	374:11 415:9	358:6,20 359:3
199:17 293:13	233:17 253:15	person 186:17	pierce 457:5	362:13 386:8
304:20 309:8	253:22 266:18	190:23 257:24	Pier's 373:12,15	389:18 395:6
309:21,24	267:5 274:13	257:24 390:16	418:24 420:12	397:18 436:24
318:11,23	275:4,21 276:5	478:2	pill 333:2	462:1 463:18
332:12 341:16	276:24 277:8	personal 4:5	pills 56:2 65:7	465:1 478:1
342:19 343:24	277:19 328:12	185:13 416:21	Pisano 300:4	plaintiff's
344:14 346:13	336:6 338:4,11	personally 155:9	place 13:7 44:5	219:20
347:22 358:15	338:15 345:1	185:23 191:19	355:8 485:8	plan 359:24
366:10 392:16	348:4 361:6,12	291:10 387:24	placed 184:18	385:22 386:6
439:4,8 468:10	404:21 436:22	390:13	184:21,22	planned 359:9
percent 48:4,7	449:20 450:12	person's 184:19	186:12 212:17	plans 220:4
85:16 111:14	457:6	190:10 327:15	274:21 409:7	359:2,21 386:2
111:18,23	perineally 108:2	perspective	409:13,21	plaques 338:21
121:6 124:22	110:3 161:16	194:21,22	442:17	platy 111:1
125:4,6,10,20	208:3 241:5	pertinent 71:8	places 91:11	164:15 168:7
126:2,6,11	336:12 345:7	petition 228:22	92:18 185:15	170:3 179:2
131:8,10	346:11 357:12	229:11 232:1	341:10	284:16,16
290:23 308:23	perineum 164:3	329:12	placing 185:1	372:8 375:10
308:24 309:12	164:22 170:20	Pharmatech	plainly 88:10	375:19 377:14
309:15,21,23	179:24 190:15	3:23	plaintiff 10:5	378:14 379:7
310:9,13	193:4 194:19	Philadelphia 3:8	35:11 57:3	399:15 400:2
315:17 319:4	206:15 229:6	phone 478:2,5	95:7 107:18	400:15 401:7

404:3 455:22	416:4 427:13	possible 164:16	54:22 55:6	162:3,9,18
456:2 459:2,4	441:7 444:18	217:14 314:6	56:15,23 57:4	163:3,10 164:2
459:15 465:10	453:17	314:16 387:24	57:5,14,16,23	164:3,10,19
466:19 467:6,8	pointed 68:13	456:16,22	58:2,10,12,21	165:16,23
play 179:23	119:15 120:3,7	possibly 164:18	58:23 59:8,11	166:15 167:17
playing 399:13	121:9,16	168:8 170:9	60:6 61:5,11	169:16,22
plays 174:19	197:20 214:7	171:10 242:8	61:15,23 62:3	170:6,15,19
177:18 220:17	217:6 238:13	262:8 280:17	62:24 64:9,12	171:1,6,9,16
434:2	260:13,20	281:3,4 282:1	64:15,19 67:2	173:18 174:24
Plaza 2:9	292:2 374:5	284:18,21	67:13 106:6,23	175:13 176:2
please 9:6 37:5	pointing 230:1	401:7 402:8,15	107:1,12,22,24	176:22 177:21
230:20 231:21	230:11 300:11	402:20 403:3,8	108:9,11 109:3	178:15,23
275:23 301:6	points 103:22	403:12 404:3,9	109:22 110:2	179:1,24 180:8
340:23 394:6	340:9 341:22	434:6,8 458:14	110:17,19,24	180:17,23
418:18 455:11	policy 50:19,22	459:3	111:8,12,15,18	181:4,11
plenty 129:14	pooled 261:11	posted 351:14	113:18 114:13	182:14,16,20
pleura 184:22	261:19,24	462:19	119:9 120:11	183:6 190:17
184:23 185:2	262:6 265:11	postmenopausal	121:6,20	191:7,11,14
186:19 189:7	pooling 261:2	321:5 337:17	123:22 124:2	193:21 194:9
pleural 160:20	popular 55:2,22	369:2	124:11,22	194:17,18
185:12,16	55:23 56:1	postmenopause	125:20 126:23	197:1,4 199:6
186:8 338:21	462:9	316:19	127:1,7 128:1	200:23 201:10
pleurodesis	population	post-2014	128:22 129:2	201:22 202:8
184:15 185:7	292:19 295:16	312:17 313:10	129:19 130:2	203:22,24
185:14,17,21	298:10,11,23	potent 458:21	130:13,23	204:18 205:5
186:4,11,12	299:4 352:18	potential 44:24	131:1,3,10,14	205:12,19,21
187:3,11,15	370:10	62:24 200:12	131:19 133:16	206:2,7 207:17
188:2,11,15	portion 425:19	206:1,1,21	134:5,8,12,17	208:3,13,23
189:1,16	471:7	227:5 329:4	134:22 135:21	209:2,5,10,12
190:16,20,24	pose 295:13	343:8 423:13	135:23 136:19	209:13,14,17
191:8,11	position 88:7,13	430:2,9	138:16 139:16	209:21 220:18
217:13,16	193:3 282:18	potentially	140:24 142:16	221:14 234:20
PLM 129:3	444:10,22	180:18 209:10	142:19,21	234:23 237:19
Plunkett 95:15	positive 145:13	351:18 401:3	143:5,6 144:2	241:5 251:22
95:23	145:19 146:13	438:5	144:7,8 145:8	257:5 264:10
plus 167:7	146:23 147:8	powder 1:3 7:18	145:10,11,16	267:6,15 268:5
point 96:5	147:13 148:17	14:1,22,24	146:5,12,22	274:2 280:13
135:17 169:21	159:5,19 264:9	15:7,10,12,13	147:6,8,11,16	281:10 282:6
179:18 212:4	265:3 369:8	15:17,22 16:1	147:19 148:13	290:4,24
230:12 239:16	426:4 428:24	16:4,5,7,12	149:1,5,12	292:14,20
278:22 291:11	452:17	17:1,21 19:15	150:2,3,9,15	293:21 294:24
293:15 305:4	possession	20:2 24:22	150:21 151:4,9	295:18 296:16
318:3 324:22	406:15	25:2,5,24 26:6	151:24 152:6	297:9,13 298:9
325:3 352:14	possibility 16:8	26:24 27:17	152:15,22,24	298:11 301:15
381:5 382:1	208:17 310:24	28:2,3,4 43:7	153:3,11,18,24	301:16 302:2
394:1 415:13	365:6	45:7 54:14,17	154:6 161:15	302:12,22,23

304:21 308:3	401:24 404:22	60:11 73:3	pretty 171:12	22:19
308:22 309:9	405:3,11	74:3 133:23	369:10	procedure
311:6 315:15	407:16 409:20	286:16 348:3,6	prevalences	184:18 454:15
315:18,24	416:6,16	348:13 349:9	307:7 308:4	454:17
316:5,23	420:15,24	350:3 359:11	prevent 45:18	PROCEEDIN...
317:12,19	423:9 433:9	359:20 362:24	Prevention 8:8	5:4 9:1
318:10,12,23	434:13 438:17	practiced 59:20	233:24 272:9	process 33:24
319:4 320:19	447:14,15,17	60:3	previously 80:2	34:3,13 35:2,8
320:22 321:17	448:3,5 456:18	practices 1:4	200:10 295:21	177:5 263:17
323:1,2,10,19	458:1,5,6,6,10	43:19 46:4	428:6 463:5	produced 66:6
324:5 325:7,14	459:6 461:7	practicing 20:22	primary 8:7	67:21 179:19
327:16,16,23	464:6,16,21	33:15 48:6,11	186:17 257:6	179:20
328:23 331:12	465:3,5,9,16	62:23 228:9	272:8 293:14	produces 185:7
333:2 334:2	465:21 466:3,5	286:11 292:8	293:19 302:20	215:16
336:6,12,21,23	466:8,15,24	practitioner	302:20	product 14:1,24
337:9,23 338:6	467:12,13,22	42:16 348:8,10	Princeton 2:20	15:8,10,12
339:6,12,17	468:3,10,14	preamble 6:10	130:2	16:5,12 28:3
340:6 341:20	470:3 471:5	31:8,17,20	principles 33:18	58:23 111:8
342:5 343:13	472:12 474:1,4	33:2,10 270:4	printed 113:10	114:24 119:7
343:17,21	477:7	precancerous	printout 12:11	123:15 124:11
344:2,21 345:1	powdered 28:6	326:13 409:23	113:15 128:19	124:21 129:2
345:6,18,23	28:24	preference	272:7	136:14 142:21
346:10,15	powders 22:4	200:4	prior 11:24	145:3,10,11
348:4,15	25:11 26:15	preliminary	19:21 48:5	147:7,15
349:10 350:5,8	27:10 29:19,24	140:8	57:2,9,13,19	148:18 149:1,5
352:10 356:14	30:24 415:16	preparatory	59:7,12 60:3,9	151:4,24
356:18,19	434:15 435:17	399:20	60:14 62:5	152:22,24
357:3,11,21,24	436:13 437:2	prepare 105:10	94:20 137:6	153:16,18
359:14,22	437:19	prepared 39:8	281:21 288:3	162:4,10 163:3
361:6,12 362:5	powder's 124:20	preparing 97:16	304:17 308:20	164:3,19,20
362:13 363:16	128:5	presence 133:16	321:18 350:2	165:16 167:17
363:20 368:6	power 99:19	175:23 176:2	355:20,23	171:1 174:11
371:24 372:2,7	101:14 255:16	180:7 459:22	357:6,16 470:3	176:2 177:21
372:17 373:4	255:19,21	462:20	485:4	178:23 180:18
373:10,17,24	256:3,23 257:1	present 45:15	private 351:13	180:23 181:11
374:8,15,20	257:14,16	85:21,22 87:18	probably 10:11	182:7,17 184:9
375:7,23 376:6	259:4,9,12,15	180:23 258:16	26:19 47:7	190:17 197:1
376:23 377:7	259:19 261:11	460:5	65:22 69:12	201:23 220:19
377:19,23	261:14,18,24	presentation	141:8 241:17	290:4 299:4
378:13,19	262:6 266:5	54:17	283:24 360:14	327:16,23
379:11,13,17	267:22	presented	361:15 366:10	334:21,21
380:9 381:2,6	powered 296:14	233:15	379:19 389:4	335:1 372:7
381:8,11,15	practice 16:14	press 55:2,23	402:16 403:15	376:23 377:19
384:5 385:3,14	46:22 47:14	56:1 462:9,9	475:10	377:24 401:16
399:14,23	48:2,7 49:9	presumed	procancer 22:23	402:6,11
400:19 401:14	59:9,13 60:5	163:24	procancerous	404:14,22

405:7,11,17,19 405:20,21,22 406:2 421:4,9 421:11 458:10 458:16,19,22 459:1,6 464:21 466:3,5,24 467:12,13,15 467:22 468:3 468:24 469:4,6 474:2 production 39:24 74:12 92:7,22 products 1:3,4 4:5 16:3 62:3 64:13 113:18 120:12 121:6 121:21 125:21 128:22 129:19 136:13 143:20 144:1,2,7,9,11 144:15,21,23 145:16,20 146:5,8,13,15 146:19,23 147:16,19 148:1,2,2,13 149:12 150:3,9 150:15,21 154:5,10 165:24 199:6 372:11 373:17 374:1 375:7,23 376:6 377:16 377:22 378:13 378:19 379:12 399:14,23 400:1,19,24 401:14,24 405:3 416:6,21 420:24 433:10 435:19 442:24 447:14,15 448:3,21 449:1 456:19 458:1,5	461:7 465:16 465:21 467:12 467:22 468:15 470:3 471:5,9 professional 8:8 272:10 362:19 472:16 473:15 professor 444:11 professorship 444:17 progression 174:20 175:8 176:19 180:16 184:7 376:12 389:5 proinflammat... 180:14 184:6 project 12:23 proliferation 409:23 promise 212:4 prompted 481:7 prone 254:2,9 382:3 prophylactic 473:7 proposed 90:22 220:8 226:4 proposition 20:6 23:11,17 propounded 486:6 prospective 28:14 197:16 254:21 255:1 256:14,20 261:12,24 262:7 265:16 266:15 267:14 282:4,11 288:21 289:9 290:8,12 291:21 316:17 317:22 318:2,8 370:17	protect 364:21 365:2 protection 298:18 protocol 300:10 prove 413:12 448:23 provide 40:16 70:2,9 80:17 88:19 231:22 provided 12:2 12:19 14:8,10 32:20 33:2 34:8 35:1,11 36:16 39:12 40:13 65:15 69:8 70:6,8,8 72:17,20,23 79:20,23 80:2 80:10,14 82:6 83:1,13 84:11 84:22 85:1 90:23 92:4,13 92:14,20 93:8 94:9 106:3 113:23 114:5 139:24 258:20 260:8 414:15 427:6,9 483:13 Provista 48:22 48:24 49:6,19 49:20 50:1,24 51:2 478:23 PTI 3:23 public 1:19 9:10 30:4,15 32:6 64:16 270:14 270:21 271:7 280:12 281:8 486:19 publication 33:20,22 91:5 91:6 103:14 200:3 235:14 258:5 280:5 283:7 360:2	386:4 publications 54:9 64:1 publicity 310:22 publicize 359:22 publicly 91:3,8 104:10 361:4 publish 64:8 published 34:12 34:17,19,22 54:13 63:12,21 64:11 106:13 106:15 141:18 234:22 235:13 235:16,18 236:6 237:1 245:21 252:11 256:7 257:13 257:16 278:21 279:5 280:8 282:8,14 287:13,17 311:24 329:17 382:6 391:7 412:16 462:13 469:22 PubMed 13:12 14:5 pull 128:13 173:11 292:22 423:19 470:22 pulled 14:8 28:10 31:21 32:1 98:10 113:2 143:8 461:5 467:21 pulmonologist 186:14,16 purchased 136:19 pure 375:10 455:22 purported 262:24 448:1 455:17 purpose 65:5	185:1 219:23 295:4 purposes 37:12 39:9 93:3 178:12 336:10 pursuant 1:13 pursuing 363:6 push 473:6 pushed 195:15 put 24:12 34:3 83:23 108:19 120:16 148:6 155:9 185:17 270:9 296:19 334:11 335:11 338:3 387:6 392:12 410:12 451:16 puts 56:24 164:21 206:3 335:7 putting 219:6,10 256:17 p.m 213:12,13 213:14,16 252:21,22,23 253:2 315:7,8 315:9,11 378:4 378:5,6,9 388:10,11,12 388:14 444:2,3 444:4,6 445:18 445:19,20,22 461:17,18,19 461:21 484:5,7
<hr/>				
Q				
qualified 133:15				
quality 111:7				
198:19 199:16				
200:8 207:13				
239:18 245:19				
246:8 251:16				
260:20 262:11				
263:10 292:3				
293:4 295:13				

311:23 470:9 quantification 452:15 463:19 463:23 464:2 quantify 107:11 107:24 108:10 150:1,7 161:19 162:2,15,23 181:8 189:4 191:13 218:19 328:11 334:22 335:2,5,16 336:2 373:3,5 375:1 quantitate 333:24 334:8 quantities 185:8 quantity 107:1 476:18 queried 109:10 queries 99:20 266:6 query 304:24 question 13:24 13:24 14:17,20 15:1 24:12,20 25:21 26:22 27:20 32:1 33:7 39:3,5 44:12 52:12,14 58:16 60:14 61:11,17 62:16 65:10 66:16 67:11 77:15 82:8 83:3 84:6 84:8,16 85:3,6 85:11,13 86:9 86:22 87:4 88:2,15,24,24 89:2,5,8 92:19 106:1,4,5 107:19,23 115:13,18 119:13 120:19 121:3 122:19 122:23 123:2,6	123:11 129:15 129:17 137:24 138:4,5,7 139:1,3 142:1 144:4 146:20 149:10,19,21 150:18,19,23 152:8 156:19 163:9 178:8 179:17 180:12 184:3 192:20 202:16 203:4 203:10,14 208:11,12 215:4 230:20 233:10,11 245:24 247:4 248:24 255:20 255:23 256:8 256:10 257:12 263:21 266:11 266:12 267:9 267:12,13 268:3,18 269:5 269:10,12,14 269:18,24 275:23 277:21 289:2 291:9,15 294:18 295:14 295:20 296:14 296:20 299:9 299:15 300:7 300:13,17,24 301:3,12 303:22 310:8 312:20,22 318:15 320:16 321:11 323:17 334:10 338:14 339:16 340:23 342:13 343:11 343:14 344:4,8 345:5 346:10 372:22 377:11 378:17 380:5 387:22 392:15	403:21 422:11 422:14 436:8 439:9 444:8 458:9 460:2 468:22 472:22 482:7,16,19 questionable 86:13 questioning 371:1 380:6 385:21 questions 9:18 10:18,24 24:5 24:16 33:16 38:1 41:6 64:18,22 65:3 65:8 82:5,19 83:5 84:19 86:2 89:6 109:9 120:15 143:11 149:17 198:11 203:1 231:3,7,13,19 245:14 266:2 266:24 267:24 269:7 289:9,12 291:12,13 389:3 398:3 399:12 401:21 424:18 445:14 446:3,7 449:15 451:18,22 452:10 453:20 454:20 456:11 457:23 458:2 462:1,4 463:10 469:9 470:17 478:10 482:5 483:19 486:6 question's 26:11 26:19 quick 79:10 88:15 371:21 443:24 444:8 quite 410:16 quote 63:2 104:6	quoted 194:16 quotes 98:10,13 104:14 219:6 quote/unquote 199:15 <hr/> R <hr/> R 2:1,13 3:1,11 4:1,6,6 radicals 407:1 radioactive 192:7 raised 20:7 65:11 230:24 363:5 364:3,10 raises 103:22 Ramirez 4:7 ran 51:13 random 369:23 randomized 28:13 range 287:24 288:5 347:10 347:13 371:12 rappel@seyfa... 4:3 rare 254:20 255:7 267:7 410:16 rate 292:9 358:9 358:13,17 Rates 8:13 ratio 262:24 313:24 368:10 ratios 263:12,15 263:19 307:15 311:2 ratio's 369:14 rats 192:18 rat's 409:22 raw 405:13 471:4 reach 208:24 209:14 336:24 345:2 437:14 457:24	reached 457:15 reaches 335:19 335:23,24 336:12,21 reaching 207:12 336:6 450:12 450:18 451:9 456:17 reaction 175:1 211:8 215:12 217:8,15,17,19 217:20 409:2 409:16 reactions 23:15 215:1 407:18 read 13:7 24:11 31:19 70:24 71:2 72:8 94:4 94:4 101:13 113:19 143:7 149:24 157:11 158:15 203:2 209:19 258:14 271:24 277:14 286:6 295:4 311:3 312:13 313:4 314:14 349:21 351:21 360:10,11,15 366:10 389:24 397:15 398:8 398:14 403:2 429:24 449:4 471:7 476:2 486:4 readers 390:4 reading 180:12 212:2 214:18 250:2 253:18 253:19 275:11 277:18 297:7 308:1 310:20 328:18 349:22 376:8 390:16 429:12,15 reads 389:24
--	---	--	---	--

ready 65:21	255:12 257:18	recommendati...	69:23 70:12,15	291:3,5 335:6
real 52:13 79:9	257:20,23	472:8 473:16	70:16 71:4	335:11 370:10
369:4 371:21	292:23 302:12	recommended	75:22 95:16,19	432:5
443:24	303:23 304:3,9	350:9 393:10	112:13 141:10	refers 431:4
realized 286:8	304:15 305:11	472:2	270:13,19	refresh 198:10
really 16:6	305:17 306:5,6	reconcile 292:18	271:1,13	202:24
37:23 43:18,24	306:18 310:24	294:20 295:15	380:11 384:3,7	regard 229:18
47:3 53:20	311:5,10,15	298:8 299:6	450:2	453:20 470:8
152:21 183:1	312:5,12,19	record 17:11	referenced	regarding 20:7
203:10 269:18	313:18,21,24	18:24 24:2,15	25:16 76:24	30:16 44:23
298:9 300:17	340:9,15,20	37:11 39:2	77:4 92:8	54:14,17,22
342:19 345:6,8	341:2,7 347:8	40:2,11,20	194:16 229:10	55:6,17 59:8
realtime 1:18	348:14 351:11	66:3 68:12	232:7 234:17	61:5,15 63:18
24:16 149:24	354:4,10	69:11 83:24	271:14 278:3,6	63:22 86:11
485:3,18	378:15 382:22	88:6,7 89:18	363:9 375:8	88:19 128:20
reason 62:9	383:14 393:16	89:22 122:24	383:21	148:10 229:2,3
194:20 246:15	399:10 415:11	123:6,17	references 13:9	229:4 261:20
264:16,16,20	432:7 446:7	130:15 135:15	14:6,7,8 17:6	361:12 389:13
264:24 295:23	448:5,8 449:17	139:7,12	68:9 69:5,7	393:3 394:4
298:20 306:8	451:21 452:13	213:12,16	91:11 92:17	395:1 450:12
318:22 361:24	452:17 458:2	216:7,11	113:7 142:3,12	452:1 462:2,3
366:2	462:4 463:8,12	244:24 252:21	142:14,17	462:10 463:11
reasonable	471:10 478:12	253:2 258:15	157:14 158:16	Registered 1:17
284:23 400:11	receipt 66:9	260:15 294:17	208:8 275:17	485:3,17
reasoning 29:18	receive 94:13	300:12,21	360:1 449:23	regular 60:5,11
reasons 185:6,9	received 35:20	315:7,11 366:8	450:8,11,16	133:22
218:10 270:18	41:17 94:16	378:4,9 388:10	451:1,6 469:21	regularly 170:21
280:24 369:19	114:8 174:2	388:14 424:16	483:1,11,12	Reid 158:14
REATH 3:6	395:22 396:5	424:19,23	referencing	163:20
recalculate	453:21	425:18 430:1	429:19 430:13	rejected 222:15
262:16	receives 34:14	443:20 444:2,6	referred 121:15	222:19,23
recalculated	Recess 89:19	445:16,18,22	163:19 172:5	relate 205:17
263:23	139:8 213:13	461:17,21	185:22 246:1	324:13,17
recall 29:20 30:2	252:22 315:8	484:1,4	380:3 415:9	355:16
50:15,16,18	378:5 388:11	records 18:17	431:20 443:9	related 20:15
56:6,9 61:10	444:3 445:19	155:23	447:14 459:15	175:6 180:15
65:9,14 66:22	461:18	reduce 56:3	477:21	197:24 199:6
74:7 75:3,5	recipient 353:16	reduces 195:4	referring 44:15	209:20 311:10
77:5,17 78:22	recognize	reduction 65:6	79:3 102:3	340:1 358:1
82:3 94:15	360:23	REES 3:11	112:2 117:9	361:4 376:12
114:1 124:6	recognized	refer 128:24	125:14 132:7	430:17
128:2 129:21	154:18	344:14 365:20	179:5 185:15	relates 1:6 14:20
154:23 155:3	recollection 45:5	452:5 453:18	186:3,7 187:20	18:3 30:23
155:20 173:7	50:21 210:3	469:5	207:3 216:7	32:19 35:3
202:6 254:2,9	recommend	reference 16:18	222:20 228:21	36:2 167:16
254:14 255:9	432:20 473:6	16:21 68:6,8	260:2 287:8,24	188:10 190:19

204:17 226:4	87:4,11 96:18	371:19 383:4	95:20 96:16	482:11,22,24
226:14 232:22	96:23 158:7	399:5,7 423:22	97:4,9,11,16	483:6,11
237:6 243:17	172:16 173:10	464:1 469:10	98:7,18,19	reported 124:15
253:14 282:16	208:22 217:21	481:6	99:6,9,11,14	211:6 216:13
284:5 285:2	218:3 337:7	remind 10:14	100:15,20	268:6 291:6
310:6 314:10	380:24 467:23	303:16	102:12 104:2,9	292:7 294:21
324:12 341:4	relying 16:16,23	removal 473:7	104:14,17	295:12 296:20
367:3 368:3	23:16 25:10,23	removed 25:8,12	105:7,10,12,17	304:21 308:16
371:23 374:12	27:9 75:19	26:24 193:8	105:23 111:5	308:23 309:1
375:4 465:8	83:2,7 84:4,12	195:3 472:4	112:4,13 113:1	309:10,22
relationship 7:7	85:10,20,24	473:19	125:10,15,22	310:1,9 322:8
126:22 254:19	86:10,24 88:21	renal 160:20	126:7 127:14	324:4 325:19
257:9 259:16	95:7 112:23	RENEE 4:2	128:14,21	371:13
296:15 302:22	117:23 136:18	reorient 276:2	129:13 130:8	reporter 1:17,18
352:13 383:22	137:11,15	repeat 24:20	135:3 136:5,18	9:6 10:17
429:9 445:7	139:17,21	107:19 275:22	137:1 155:12	82:14 202:12
relative 201:16	140:23 141:14	340:22	171:21,22,23	242:20 430:5
259:6 262:1,7	142:7,11,19	repeated 26:20	172:11,14,15	460:10 485:3,4
287:22 288:4,8	143:24 145:6	189:2	172:17,18,21	485:17,18,18
346:22,24	146:3 164:6,13	repeating	172:23 173:1,2	reporter's 461:2
347:4,9 355:18	169:13 174:21	165:13	173:4,10	reporting 263:5
355:24 368:5	175:5,23 176:1	rephrase 82:9	174:10 175:17	263:19 311:19
368:22 371:18	178:13,19,20	82:12 83:3	175:21 177:16	reports 93:14
485:11,12	180:6 236:16	85:11 138:7	178:7 193:16	94:8,18,22
relatives 356:4	373:8,15,22	152:10 246:3	198:17 207:4	95:2 96:1,7,10
released 433:1	374:5 375:5	344:7	208:1,7 209:4	96:10,12,14,24
relevance 385:8	382:6 459:13	rephrased 138:6	209:11 221:17	111:22 112:3
relevant 225:2	463:18 464:4	replacement	222:19,21	129:2 131:7
reliable 13:3	482:20	273:19 356:21	234:16 242:12	137:6 138:22
30:4,8 105:3	Remain 8:10	369:3	245:17 246:2,6	139:18 140:22
229:1 272:20	295:2	report 6:14,16	255:14 259:14	143:19 227:4
272:24 368:15	remaining 38:12	13:16 14:21	260:3,4 261:13	262:13,23
reliance 263:21	remains 147:24	15:2 16:19,22	263:11 264:12	292:14 374:7
367:5,8 374:4	187:3 298:2	17:3,7 25:15	264:17 270:12	375:13
relied 87:17	remark 239:15	25:16 32:20,21	286:10 289:15	represent 9:17
91:21 127:13	remember 11:23	36:3,13 53:6	290:21 297:7	128:21 140:8
161:10,11	24:23 44:6,7	65:15 66:12,19	316:12 333:6	388:20
174:9 450:11	47:24 65:3,8	68:8,19,21	334:13 358:1	representation
451:9 470:4	90:13 94:1,5	69:5,15,18,21	360:1 367:13	247:13
relies 85:15	94:19 97:12	70:12,13,17,19	367:19 376:9	representative
86:19 88:9	143:21 155:14	72:4,7 78:5	380:7,13 384:4	114:22
91:15 156:4	172:9 191:12	79:11,12 81:6	385:24 420:12	representing
158:1 160:22	198:5 211:8	81:15,20 90:6	425:12 452:11	12:1
346:19	221:8 269:21	90:22 92:9	452:14 468:6,8	Reprint 6:7
rely 26:14 73:11	270:16 304:21	93:10 94:21	469:14,21	reproductive
73:18 76:15	347:7 352:11	95:6,11,16,19	470:5 473:23	6:11 395:11

396:22 397:16 398:11,22 399:8 436:14 436:19 437:15 437:15 438:18 439:22 440:22 474:3 reputable 227:18 228:16 229:19 request 12:3 39:24 40:6 41:3 60:16 61:6,9 72:19 74:24 92:7,21 394:6 requested 65:19 66:2 72:23 75:4 395:11 396:21 requests 66:6 67:18 68:3 required 183:16 386:20 391:2 research 7:17,17 12:23 20:23 31:2 32:5,9,16 56:5 64:12 220:2 222:7 223:11 224:5 395:21 478:9 479:22 480:5 480:12 481:9 researched 106:7 researching 63:6 respected 32:6 respond 26:22 120:19 230:19 295:22 responds 108:24 response 22:19 22:23 68:2 181:13 184:19 185:3,8 188:2	188:7 189:17 189:22 209:22 210:2 211:24 212:1,9,14 214:14,20,24 215:17 216:14 216:19 217:24 217:24 218:5,6 218:9,13 219:4 219:14 220:23 229:11,14 232:1 327:15 329:8,10,13,19 329:21,24 330:5 331:21 333:7 334:11 337:20 367:5,9 367:11 399:12 responsible 437:19 rest 290:2 311:3 restate 151:1 422:11 result 18:5 148:17 259:7 302:12 325:14 411:22,24 438:19 474:3 resulted 324:7 448:4 resulting 412:9 results 106:11 114:15 115:5 118:19 140:9 145:19 146:14 146:24 153:4 211:13 212:2 246:18 255:12 258:21 259:11 262:17 275:6 277:11,16 303:9,17 305:2 306:17,18,23 312:4 313:12 314:7,7,17 341:21 448:15	448:19,23 resumé 54:12 retail 406:5 retained 389:18 retrograde 192:10 223:22 227:10,21 228:12 430:2,9 430:20 440:3 retrospective 7:5 254:1 retrospectively 28:23 revealed 117:15 415:24 review 7:22 12:21 31:2,17 31:23,24 34:2 35:7 56:22 62:7 73:4 75:12 79:19,22 80:20 81:16 84:23 90:10,18 91:10 124:1 128:24 129:9 135:10 136:17 141:20,22 154:15 155:8 155:10 157:5 172:23 178:6 197:15 227:5 229:1,14 231:24 232:18 234:7,9 235:8 235:23,24 238:16 245:5 247:7 255:10 271:22 278:8 278:16,17,21 279:5,18,22 281:1,19,21 285:20,24 286:8 289:6 303:24 306:21 313:16 329:6 338:1,9 349:10	349:15,19 357:7 360:1,8 362:9,11 364:15 368:4 369:7 382:12 385:23 389:10 391:16,19 392:11,16 398:17 446:11 455:24 reviewed 12:20 18:2 29:16 34:9,13 35:18 35:21 57:10 60:15,20,24 61:4,14,20 62:4 76:13 81:23 90:5,15 91:14,16,17,18 93:19,24 94:2 120:2 136:4 141:17 154:13 155:15 157:21 158:14,18 188:10 224:10 224:10 225:23 228:8 233:6 256:5 271:18 282:20 308:11 312:23 357:19 361:11,16,17 365:7,13,14,17 366:24 374:3 384:10 391:11 391:12,23 394:4 450:17 451:8 476:12 reviewer 392:4 393:10,12 reviewers 278:24 393:8 reviewer's 392:14 reviewing 20:21 56:18,21 57:19 58:5 59:7,12	59:19 60:9,14 62:10 71:8 72:3 108:14 109:8 124:6 152:20 173:4 187:16 250:9 257:18,22 306:19 312:6 348:19 349:24 383:14 469:23 reviews 17:5 19:4 136:24 141:12,24 144:5 202:17 203:5 208:6 216:2 233:5 247:18 revising 392:22 revisions 97:24 re-ask 149:23 re-review 263:15 re-reviewed 31:21 riding 195:18 436:16 right 14:19,22 15:4 17:19 19:2 21:14 24:7,17 25:19 28:13 34:18,20 35:24 37:4 38:19 42:8,9 44:24 49:13 50:1 51:22 54:3 55:3 63:2 64:24 66:8 69:6 73:19 74:4 93:16 94:10 95:8,20 96:3 98:15 99:15 101:13 103:5,18 105:4 105:8,13,15 111:1 112:10 113:6 114:7
---	--	---	--	--

115:19 120:8 121:11,21 123:15 126:8 127:14 129:24 131:22 133:13 134:18 141:9 142:16 143:15 145:20 146:20 148:19 159:8 159:13,23 170:16 172:11 182:14 184:23 185:8,21 186:4 186:15 187:17 187:24 188:3,7 189:18 190:11 190:21 193:18 193:23 195:24 196:10 197:20 198:19 199:17 200:23 202:3,9 207:19 209:7 214:15 215:2,5 219:21 221:21 221:24 226:14 227:11,18,22 228:22 229:11 231:1,15 232:8 233:12,17 236:9 237:23 238:14 239:8 239:19 240:1 240:11,15 252:12,12 266:24 274:7 275:20 276:13 276:15,20 279:6 282:12 285:4 288:1,21 289:16 292:4 293:13,22 294:2 297:1,10 297:23 301:21 305:7,22 306:6 306:12 309:1 309:11,23	310:1,10,13 316:1,8 318:13 320:3 321:7,13 322:3 324:5,14 330:5,11,16,24 331:9,20 332:5 333:8,14,20 334:16 335:4,8 335:19 336:13 344:22 345:24 347:19 348:22 349:20 351:9 352:1 353:5,18 355:6,7,11,18 356:1,5 357:9 358:5,8,23,24 359:7 362:15 363:11,16,21 366:18 367:5 367:15 370:11 370:18 372:17 374:15 375:1 376:19 377:7 380:10 383:12 384:8,17 387:18 398:23 399:15,16 413:11 423:23 424:6 425:9 432:23 442:12 448:10 464:17 465:5 468:6 472:23 475:20 481:23 483:8 right-hand 425:24 429:7 Rigler 112:17 125:15 373:20 373:22 452:23 453:16,19 463:12 Rigler's 452:11 452:14 Rio 471:16,23 risen 361:23 risk 8:5,11,12	18:4 19:12,19 31:10 43:6 45:6 56:3,7,24 57:23 58:23 62:7 64:23 65:6 90:7 108:21 110:4 138:15 152:24 153:11 154:11 160:14,18,19 163:23 164:23 164:23 165:18 166:7,10,15 167:1,19 169:17 174:15 176:4,9,16 179:24 180:9 181:17 190:5 195:5,24 196:9 197:3 200:22 201:16 202:21 203:22 204:10 205:4 208:14 219:9 234:20 234:24 241:6 241:23 248:19 249:20 251:21 259:6 262:1,7 265:8,10,16 266:17 267:10 267:15 270:15 271:4 273:7,13 274:1,6,17 275:5 277:9 282:5,12 288:5 290:9,23 291:17 293:21 295:3,5 298:17 298:21,22,23 298:24 317:17 327:20,21 328:4,6 330:10 331:2,4,13 337:11,15 338:3 339:19 352:15 354:24	355:3,9,12,16 356:12,16 359:17,17 360:22 361:7 368:5,22 369:2 369:4 371:4,10 371:18 376:10 376:24 385:8 387:16,24 401:1 404:20 405:6 422:17 422:23 423:5,9 438:5 446:22 446:24 447:2,5 447:8,11 472:11,11,13 472:24 473:5,9 risks 6:9,21 7:12 8:21 287:22 288:8 328:7 346:22,24 347:4,9 road 188:23 Robert 480:10 ROBINSON 2:8 robust 221:18 Rohl 143:1,5 145:6,19 146:4 146:14,24 147:20 148:10 148:16 role 174:19 177:18 179:23 220:17 399:14 434:3 room 475:20 476:14 route 346:12 routes 456:16,22 routine 263:14 350:6 routinely 133:7 133:11 206:14 272:18 390:9 398:13,17 rule 6:14,16	84:20 307:14 420:22 ruled 284:23 314:1 rules 10:12 83:12 84:9 87:2 88:11 299:19 300:19 389:23 ruling 206:14 rung 383:17 running 28:12 <hr/> S S 2:1 3:1 4:1 7:9 sacrificed 410:5 Saed 35:17 36:4 219:20 235:4 235:13 381:1 392:4 393:6 394:4,24 395:15 398:5 478:5 479:21 480:21 481:3 481:16 482:2 Saed's 219:16 220:15,20 380:21 381:4 381:24 382:5 382:11 391:5 393:3 394:10 395:5 397:16 425:10 480:9 safe 109:19 110:8,11 151:20 183:1 183:18 184:11 184:12 SALES 1:4 sample 122:11 151:3 153:19 154:8 170:5 415:14,24 418:10 419:3 samples 123:13 125:3 133:15
---	---	---	---	--

135:7,11,22,23	396:5 397:2	361:10 364:18	91:7 93:20	426:8,18
136:5 137:12	419:3,13,18	395:11 396:22	94:22 95:1	429:14 439:9
416:5 420:14	425:24 431:12	397:16	96:13 98:1,14	445:6 450:7
448:18,20	447:21 448:16	score 31:2	99:16,22	454:3 455:8
459:7,14,22	448:22 467:17	241:24 284:17	101:24 102:9	478:22
460:6,9,20	scar 408:18	screen 23:20	102:15,18	seeing 169:8
Samuel 7:15	Schildkraut	screening 45:16	103:1,4,8,12	228:11 343:15
San 2:15	234:18,18	472:23	103:12 105:20	347:8
save 143:11	235:9 239:17	SCULLY 3:11	112:19 113:9	seen 11:18 37:23
saw 11:22 113:1	239:23 240:6	search 13:12	113:21 114:2	55:1 58:7
125:3,3,6	241:19 278:12	91:7	115:4 118:22	93:14 97:1
126:2,11	280:8 293:16	searching 14:5	118:22 120:6	111:5,13,16,22
130:19 155:12	297:17 302:3,7	second 17:3	129:12 133:4	131:7,8,17
173:2 198:3	302:11 303:5	23:12 112:5	135:20 137:3	134:13,23
215:11 268:4	304:1,16	117:10 141:23	143:10 168:20	135:3,19
350:7 399:9	305:11 306:4	159:1 169:2	171:22 172:13	182:15 190:4
414:23,24	311:11 329:22	208:5 210:22	172:14,20,24	287:22 375:12
432:13,13	451:3,15	218:14 252:19	181:16 188:6	375:13 378:22
saying 29:12,13	school 130:3	258:5 266:7	198:1 201:1,2	379:22 382:13
34:7 60:14	133:21	294:3 306:17	202:21 213:4	387:14 393:11
92:13 125:5	science 29:6,23	306:22 310:21	216:18 218:9	393:15 410:7
146:16 162:9	Sciences 6:11	342:17 355:20	218:12 224:10	410:12 413:2
176:16 177:15	398:11,22	388:6 418:23	226:7 227:4	438:2 440:15
191:5 208:10	399:8	443:20 452:9	230:17,18	445:1,4 476:1
208:19 213:3,4	scientific 25:23	460:11,22	244:22 245:15	476:11,16
222:10 242:7	26:13 27:8,21	461:15	246:14,16	477:20
282:24 298:8	27:22 30:17	secondarily	247:19,23	segments 55:3
325:6,11 397:7	32:11 104:24	220:24 381:23	250:7 254:3,4	select 79:18,22
397:8 403:11	162:14,22	secondary	262:2 263:1,22	80:20 414:20
403:13 407:9	163:14 165:5	257:10 293:15	272:10 275:8	selecting 251:15
459:14	166:12 167:20	409:1	275:12 278:5	selection 99:20
says 27:17 68:19	168:21 169:14	section 68:19	279:1,3,11	self-reported
86:13 91:5	174:22 175:11	218:16 225:1	291:1,8 295:24	328:23
99:15,18	176:10 177:3	258:9,12	301:15 303:21	self-reporting
110:10 119:2,4	179:11 183:20	277:19 278:22	304:24 305:1,3	329:2
119:16,24	192:21 194:8	278:24 306:23	306:20 307:3	sell 406:11
161:5 169:5	206:19 208:2	320:18 355:4	307:21 309:5,6	sells 146:22
175:6 177:16	279:17 328:10	449:16,20,24	309:19 310:16	SEM 133:23
179:18 203:15	336:4 337:6	450:17	319:14 330:10	seminars 63:17
222:3,11 225:8	386:24	sector 351:13	353:8 370:4	send 39:16 96:9
228:17 233:22	scientifically	see 21:3,4,6	383:6 386:20	senior 220:22
262:2 295:2	105:3	23:22 28:7,23	391:14 394:19	sense 337:21
306:20 308:1	scientist 244:2	31:23 37:5	401:2,4,6,8	341:8,15 443:4
351:22 363:24	415:9	48:9 51:2	415:22 418:6	sensitivity
391:15 394:20	scientists 30:14	53:18 62:19	419:2,6,7	327:20 335:24
394:23 395:13	32:10 286:22	72:13 79:14	424:14 425:23	sent 37:18 40:1

96:6,10,11 393:6 sentence 99:16 100:2 101:12 103:13,15 222:3,11 232:7 233:23 310:21 448:22 449:5 sentences 102:18 103:4 separate 72:5 153:17 166:8 382:13 402:11 separated 247:20 250:7 separately 113:11 153:1 157:10 247:22 248:13,14 separating 270:7 series 451:22 473:23 serious 384:16 serous 238:5,8 240:22,24,24 241:15,20 242:5,11 243:10 247:20 247:22,23 248:10,12,13 249:16,20 250:3 served 66:5 Services 4:8 set 47:5 71:6 398:16 414:9 414:19 485:9 setting 42:17 SEYFARTH 4:2 SGO 36:12 360:19,23 361:5,10,19 362:3,9 364:19 365:6,18 366:3 shake 107:7	110:13,13,14 shakes 110:13 Shane 4:7 share 37:7 370:1 384:14,23 SHAW 4:2 sheds 439:23 Sheet 486:7 shelf 134:12 136:15 405:23 she'll 231:21 short 99:21 185:19 257:6 266:6 267:1,22 267:23 410:5 shorten 448:18 shorter 243:19 326:18,23 shortest 267:1 Shortly 65:20 shot 310:12 show 28:2 115:5 117:8 119:2 128:9 159:24 194:9 195:23 201:15 203:21 211:7,15,16 212:14,22,24 223:21 230:14 230:22 231:8 231:10 240:12 251:20 265:3,4 282:7 291:17 329:9,21 330:4 345:21 374:19 411:2 415:15 423:4,7 434:17 468:23 473:22 474:7 showed 114:15 125:4,6 142:22 242:11 254:19 264:9 282:5,12 314:7 329:23 330:6 Shower 420:15	420:15 447:18 447:18 458:6,7 474:1,2 showing 106:16 288:15 290:22 473:24 shown 26:7 204:24 234:24 241:13 288:8 290:16 421:17 422:1,22 434:5 446:4 449:10 shows 64:1 147:15 159:17 196:9 205:3 220:22 242:9 265:8 266:16 267:14 336:5 342:9 378:22 381:9,24 474:8 shrouded 350:11 351:23 Shukla's 220:16 shut 51:5,9 sic 395:11 396:22 397:17 side 87:19 95:23 349:3 390:4,16 419:12 signature 344:15,18 signed 352:4 significance 241:18 significant 103:14 159:20 160:1,6,12,24 163:23 164:7 165:3 200:21 237:9 238:10 240:13 242:5 249:11,15,19 250:3 251:20 266:16 267:4 268:4 290:17 293:18 297:20	304:19 305:1 306:11 307:1 307:21 308:5 308:10 311:18 313:21 314:8 314:20 315:1 317:17 324:8 331:13 369:17 374:20 significantly 202:21 238:4 240:21 307:7 311:8 signs 339:21 SILVER 3:16 424:15,21 similar 32:3 38:9 94:3 102:16 106:16 259:6 331:6 similarly 217:7 simply 361:11 413:11 Simultaneous 82:13 202:11 242:19 Sinai 120:8 single 76:11,11 267:13 410:6 415:14 442:16 473:22 475:1 Sister 236:24 237:3,7,8,15 257:6 sit 326:10 475:20 site 260:8 375:16 sites 148:24 sitting 42:9 76:1 77:9,18 81:14 93:5 365:23 375:15 464:12 477:17 sixth 27:13 size 199:3 289:3	290:14 skills 46:5 skin 205:22 skip 388:24 Skipping 100:4 slide 21:8 212:24 218:8 slides 212:19 445:4,5 slight 331:2 379:20 small 47:14 68:14 138:17 151:13 202:9 241:16 293:1 369:8 375:13 smaller 457:1 Smith 6:16 98:21,23 99:2 99:6,10 100:14 100:17 Smith's 99:11 100:20 smoke 166:24 167:2 soaps 15:21 social 42:17 462:19 societies 361:19 365:1 Society 364:12 sold 148:2 405:22 sole 420:22 somebody 115:18 190:16 208:12 326:10 326:13 328:1 335:7 350:7 something's 195:14 sorry 67:10 79:12 95:21 102:12 104:5 112:5 117:13 117:14 129:6,7
---	--	---	---	--

141:10 149:20 174:11 206:13 214:4 216:3 224:20 225:6 225:15 236:3 249:22 250:15 302:10 309:18 320:13 356:22 367:2 378:2 380:17 393:14 416:11 422:13 429:11 438:12 447:7 460:12 460:14,24 461:3 472:18 472:19 sort 38:13 42:19 65:18 68:18 316:18 366:16 382:20 383:3 440:24 sound 358:5 sounds 136:8 364:2,6 source 13:3 33:1 76:11 105:3 119:17 135:20 204:8 272:20 272:24 379:10 396:10 sources 14:11 104:11 114:13 136:23 South 318:20 soybeans 435:3 speak 20:9 54:11,21 64:8 64:14,19 100:16 134:15 speaking 219:20 specific 64:18 107:17 122:13 154:8 219:8 226:21 231:7 255:20,22 289:12 291:12	340:15 359:17 393:16 452:24 453:1 specifically 19:18 20:13 31:20 48:9 56:7 75:3 78:20,24 81:9 114:4 129:21 140:6 142:18 143:8 145:2 152:21 153:8 162:19 163:9 166:17 182:24 208:8 240:19 248:10 249:14 251:23 252:7 257:23 271:1 286:17 293:17 295:9 313:3,5 354:5 389:17 400:4 432:3 434:9 specifics 313:7 specimen 212:17 212:18 213:5 218:15 specimens 214:20 379:3 spectrum 404:15 speculate 418:17 spend 97:16 173:3 203:11 spending 59:18 sperm 192:6 spoke 64:13 478:4,5 479:12 481:8 spoken 56:10 462:23 480:13 sprays 15:16 spring 364:11 Square 3:8 staff 46:19,20 standard 187:3	263:14 standing 478:22 starch 407:23 starch-based 407:16 start 9:17 14:4 70:10 87:3 224:18,24 315:18 319:4 320:22 321:15 323:10,19 355:8 460:23 started 45:8 47:10 53:9 56:18 72:6 106:4 201:10 217:11 315:24 316:4 317:8 318:12,16,18 318:21 323:15 325:15,17 348:13,14,17 348:19 349:8 starting 11:24 13:6 starts 324:24 440:19 441:8 start-up 48:21 state 1:19 66:4 180:14 184:6 221:16 255:14 289:14 290:20 355:11 381:22 382:2,3 448:11 480:2,7 stated 80:1 171:18 198:17 223:15 319:3 333:24 395:12 statement 39:2 41:10 83:23 142:20 230:1 230:24 254:13 256:22 259:13 259:16,18,22 261:19 350:17	363:15,23 365:21 states 1:1 7:6 49:8,15 124:19 449:2 statistical 238:4 240:21 241:17 242:13 259:4 290:16 297:20 305:1 308:16 statistically 160:1,6,11,24 163:22 200:21 237:9 242:5 266:16 267:4 268:4 306:11 307:1,17,20 308:4,9 311:8 311:17 314:8 314:20,24 317:16 369:17 statistician 262:3 stay 84:8 87:23 stays 22:12 Steering 2:6,11 2:16 stenographica... 485:8 stenosis 193:6 step 169:20 324:20 362:10 388:1 steps 361:21 Steven 7:15 stick 294:11 sticker 113:14 stimulation 381:23 stop 21:23 59:4 195:20 348:18 350:9 stopped 16:15 stopping 17:24 stored 135:24 stores 406:5	straight 86:16 strategies 8:16 351:2 stratified 258:19 309:7 Street 1:15 2:4 2:19 4:3 streets 474:17 strength 226:3 367:23 368:3 strengths 270:8 stress 380:20 384:6 385:15 stretched 388:2 stretched-out 387:2,8 strike 56:10 149:15 284:8 stroma 457:3 stromal 241:11 strong 226:9 368:13 stronger 160:11 strongly 159:5 426:4 428:24 structures 448:17 studied 29:6 152:15 192:7 199:8,17 243:19 244:4 256:13 412:14 412:18 413:5 421:6 432:12 438:2 439:14 studies 14:13,14 14:14 18:13 21:20 27:22 28:1 56:20 99:19 100:7 101:14,23 102:7 103:17 106:8,8,8,10 106:15 108:15 110:12 147:10 152:11,16,20
---	--	--	--	---

153:5,9 157:5	288:4,9,21,24	243:6 244:20	stuff 404:15	261:1 280:3
157:24 158:18	289:8,10,11,15	244:23 245:21	subgroup 239:3	387:15
159:6,24	289:19,20	246:2,10,13,14	248:3 303:4	suggested 21:21
160:21 161:7	290:8,12,22	246:20 247:5	305:7 317:11	62:6 438:3,23
164:8 165:3	291:6,8,16,17	247:22 248:9	subject 12:20,21	448:2
168:21 169:4	291:21 292:2	248:11 249:12	31:24 312:12	suggesting 45:10
179:11 192:16	293:3,12	249:17,24	312:19	69:13 173:22
193:17,20	311:16,21,22	250:14,22	submit 360:2,7	177:20 353:11
194:1,3,15,18	313:16 315:24	251:16 252:4	392:19 471:13	suggestion 29:10
195:23 196:14	316:17 317:22	254:21 255:1,7	submitted 39:9	40:12 454:16
197:10,14,17	318:3 325:19	256:24 257:6,7	39:20 91:5,6	Suggestions
199:5 200:4	329:17 330:3	257:8,10	94:18 96:1,12	392:22
204:23 217:13	338:10,13	258:19 259:17	233:15 391:18	suggests 58:22
217:17 219:5	341:22 345:21	259:22 260:12	391:22 448:20	148:24 163:20
227:5 234:16	346:19,23	260:19 261:20	471:9	197:2 219:5
235:7,20	368:10 369:8	263:10,21	Subscribed	254:18 412:13
236:17,23	370:11 383:10	265:13 266:8	486:15	439:10
237:11 238:3	383:22,23	267:3,14 270:7	subsequent	suing 357:20
238:11 240:16	385:1,13	270:9 281:22	19:21 38:8	Suite 2:14,19 3:8
240:21,23	387:23 406:20	292:3,4,7,23	substance	3:12,21
241:1,14,14	412:15 413:2	292:24 293:9	194:23 195:9	summary 33:9
242:4,14	413:12,17,22	293:16 295:4	286:23 455:11	100:5 260:4
244:13 245:8	413:24 422:5	295:12 296:13	458:11 478:7	278:23 420:11
245:19 246:8	422:14 423:3,7	296:19 297:17	479:20 486:7	supplemental
247:21 249:10	423:14 426:5	297:17 301:24	substances	91:11,15,20
249:15 250:5,8	428:24 434:16	302:3,20,21,24	194:18 221:11	92:1,7,11,18
250:12,21	434:22 442:23	304:13 311:4	283:19 284:5	92:20
251:4,12	456:12 468:23	313:8,19 317:3	402:9 404:10	suppliers 448:20
253:16,24	469:3,13 470:2	318:5,8 319:1	443:3 458:12	471:8
254:2,6,14,16	470:9,15	319:8 321:3,10	458:13 467:13	supplies 416:15
254:19 255:3,6	study 7:6,20	321:19 322:23	467:16 468:24	support 25:24
255:15 256:4	28:6,14,18	323:13 329:4	subtracted 72:9	27:8,21 143:24
256:10,14,20	29:11,12 108:6	329:21,22,22	subtype 240:1	145:7 146:4
256:22 257:2,3	116:16 146:14	340:8 346:8	subtypes 241:13	158:7 160:22
257:11 258:18	159:17 168:2	371:17 384:7	241:16,21	163:15 164:9
258:21,23,24	169:8 179:17	384:11 385:8	successor	165:5 166:12
259:1,5,8,9,14	192:19 199:2,4	385:11 409:21	471:16	167:20 169:14
259:23 260:21	199:15,19	410:7,11	suffering 186:18	174:22 175:12
261:14 262:11	200:8 203:12	433:11,17	sufficient	176:3,10 177:2
262:23 263:4	209:7,20	435:23 436:7	283:20 284:10	177:8,9 178:14
265:21,24	214:12 234:19	437:24 438:3	409:7	179:4 180:6
266:4,15,22	234:24 236:5	442:16 451:15	sugar 432:23	182:15 183:21
267:21 275:6	236:24 237:3,7	469:5 473:23	433:2	192:21 193:17
277:17 282:4	237:8,15,16	473:24	suggest 28:1	206:18 208:1
282:11 287:9	238:13 239:18	studying 193:21	29:5 40:18	208:21 209:12
287:11,23	241:19 242:12	220:4	160:15 220:17	214:7 232:4

234:11 275:3	411:6,6,13,18	tabbing 68:17	6:18 7:5,8,8,13	225:22 227:10
277:7 311:4	411:23 412:10	table 85:23	7:21 8:4 17:8	229:2,4,15
373:16,23	413:13 473:7	240:1 241:21	17:15 19:15	230:7 232:5,22
374:8 382:7	surgical 22:4,11	245:8 303:19	20:8 22:11,18	233:16 235:22
384:3,4 386:24	22:18 23:3,8	304:24 305:7	23:2,7 28:3	237:6 244:11
395:20 418:2	23:13 24:23	308:20 330:9	43:5 44:12	248:19 249:9
475:16	25:2,8,12 26:1	330:22 332:1	49:24 50:5,10	253:15,22
supported 29:23	26:7,15 27:1	332:11 349:3	56:15 76:6	254:8 257:9
457:9	27:10,17 28:3	483:4,11	106:20 108:21	259:3 265:17
supporting	28:18 29:19	tabs 68:21	109:3,14 111:1	271:18 274:14
121:5 221:18	30:24 407:19	Taher 90:16,22	111:2 112:17	275:4,21 276:5
supports 146:17	454:14,17	91:2,10,15,21	117:12 118:24	276:24 277:8
209:16 363:20	surprise 437:9	92:2,8,13,14	119:20 128:20	277:19 280:17
385:2 412:13	437:10	92:16 281:17	135:22 138:20	280:21 281:1
supposed 346:7	surprised	take 11:6 27:24	140:16 141:5	281:22,24
sure 23:1 24:10	100:18 129:22	42:22 44:4	141:21 142:9	284:8,11,15,16
28:16 29:4	surprising	59:15 72:2,5	153:13 161:21	284:16 285:13
32:24 79:9	101:20	72:10 85:7	162:6 164:14	285:13 289:3
80:23 82:17	survey 168:19	86:8,15 88:6	164:15 168:8,8	290:15 302:5
86:18 92:10,12	448:16	88:16 89:14	170:3,3 179:2	309:22 310:1
103:11 107:21	susceptible	99:13 104:3	179:2 184:14	310:10 315:14
108:6 116:12	337:8,10	112:8 118:20	184:18 185:6	328:12,22
119:15 120:7	suspect 167:7	128:23 129:9	185:10,21	329:6 336:17
120:21,23	178:8	139:5 196:17	186:3,11 187:2	340:11 341:5,6
121:1,5 128:12	suspected 22:5	198:7,9 210:5	187:10,15,17	342:18 358:21
189:12 204:3	338:19	210:11 211:5	187:22 188:1	359:3 362:20
205:16 231:21	swear 9:7	211:16 213:7	188:11,14,20	366:4 372:1,9
232:3 236:14	sweating 318:22	245:6,12	188:24 189:2,5	372:9 375:5,6
244:2 251:9	sworn 9:9 485:5	254:24 256:9	189:7,16 190:9	375:10,11,17
262:4 267:8	486:15	315:5 325:12	190:16,20,23	375:19,20
275:24 295:8	symposia 63:17	327:23,24	190:24 191:1	377:14,14
313:11 317:7	462:24	359:24 364:14	191:11,23	378:14,14
326:4,21	symptoms 45:16	418:7 432:19	192:1,18	379:1,2,7,7
327:14 334:1	56:4	466:4 475:1,8	199:10 204:7	381:2,6 382:7
342:2 343:20	syndrome	taken 1:13 28:5	204:13 206:20	382:14 385:1
344:3 346:6	337:14	35:24 89:19	207:1 211:7	388:20 389:11
360:9 366:11	synergism 167:8	139:8 168:2	212:9,12,13,16	389:14,19
370:24 371:22	synergistic	213:13 252:22	213:1 214:8,13	395:6 397:14
375:16 376:16	166:5 167:4,5	315:8 378:5	214:24 215:12	399:16 400:3,3
378:21 407:7	system 108:23	388:11 444:3	215:16 216:14	400:15,15
415:21 444:9	195:2 457:4	445:19 461:18	216:19 217:14	401:5,8 404:3
444:13 466:14	Systematic 7:22	485:8	217:16,22	404:5 405:13
470:2 476:1,8		takes 217:22	218:4,4,8,11	406:11,14
surgeries 408:4	T	325:20 326:12	219:17 220:6,9	408:20 409:7
surgery 28:24	T 406:23	361:19	220:23 221:6	409:13,17,21
408:8 409:2	tabbed 68:16	talc 3:14,18 6:12	224:23 225:22	410:8 415:14

416:5,15,19,20	58:12,21,23	201:10,22	362:13 363:16	105:18 208:8
417:1,2,6,19	59:8,11 60:6	202:7 205:5,12	363:20 368:6	209:1 216:4
418:5 424:10	61:5,11,15,23	205:19,20	371:24 372:6	230:23 237:14
424:12 429:10	62:3,24 64:9	206:2,7 207:16	374:8,14,20	352:15,16
429:23 430:9	64:12,15,19	208:3,13,23	376:6,23	359:16 447:4
430:20 431:2	67:2,13 106:5	209:2,5,10,12	377:19,23	talked 25:15
436:11,12	106:22 107:12	209:13,17,21	378:13,18	42:19 56:2,4,5
441:10,11	107:24 108:9	220:18 221:14	379:11,13,17	56:7 103:16
442:16 443:4	108:11 109:22	234:20,22	380:8 381:2,6	132:4,11
443:13,14,17	110:2,17,19,24	237:19 241:5	381:7,11,15	182:14 196:4
447:10,21	111:8,12,15,18	251:22 264:10	384:5 385:3,13	345:19 348:12
448:3,14,20,24	113:18 114:12	267:5,15 268:5	404:21 409:20	362:23 363:1
449:16,21	119:9 120:11	274:1 280:13	423:8 447:14	367:20 440:4
450:13 452:2	121:6,20	281:9 282:5	447:15 448:2	443:5 447:13
453:21 454:8,9	126:23 135:21	290:4,24	456:18 458:1,5	461:6 479:20
455:1,3,14,17	138:16 139:16	292:14,20	458:6,10 459:6	480:1,11
455:22 456:2	140:24 142:20	293:21 294:23	461:7 464:21	481:10
456:17 457:15	143:5 144:7	296:16 297:9	465:16 466:3,5	talking 17:7
457:19 459:2,4	145:9,11,16	297:13 298:9	466:8,15,23	24:22 28:12
459:8,16,19,23	146:12,22	298:11 301:15	467:12,13	42:24 45:8,20
460:5,8,16,20	147:16 148:13	301:16 302:2	468:3,10 470:3	102:11 107:21
462:14,20	148:24 149:5	302:12 304:21	472:12	119:23 127:5
463:1 465:10	149:12 151:4	315:15 318:9	talcum-based	131:21 162:3
465:10 466:10	151:24 152:6	318:12 320:19	400:1,23,23	196:6 209:6
466:16,19,19	152:15,22,24	321:17 322:24	talcum-dusted	217:12 229:9
467:6,6,9,9	153:3,10,18,23	323:2,10,19	28:6	231:5 232:11
469:10,15	154:6 161:15	325:7,14	talc's 474:13	232:15 240:17
471:4,8,14,24	162:3,9,18	327:16,23	talc-based	240:20 321:8,9
472:5 473:11	163:3,10 164:2	328:23 331:12	399:14,22	340:17 342:14
473:17 474:10	164:3,10,19	334:2 336:21	400:18 401:13	342:15 349:2
474:18,21	165:16 166:15	336:23 337:8	401:24 405:3	383:9 476:15
475:4,10 477:3	167:17 169:16	337:23 338:5	405:11 415:16	talks 20:13
480:18	169:22 170:15	339:5,11,17	420:23 433:8	tampons 16:2,7
talcs 471:17,21	170:19 171:1,6	340:6 341:19	434:13 435:17	436:17 438:9
talcum 1:3	171:9 173:18	342:4 343:13	436:12 437:2	tape 134:3
13:24 14:22,23	176:22 177:21	343:17,21	437:18 471:5	252:18 378:2
15:6,7,9,11,17	178:15,22	344:2,21 345:1	talc-containing	TARIQ 3:20
15:22 16:1,3,5	179:1,23	345:6,18,23	448:24	tariq.naeem@...
16:7,12 17:1	180:17,23	346:10,15	talc-dusted	3:21
17:21 24:22	181:4,11	348:4,15	16:10 18:5,14	task 266:18
25:2,4 28:2,3	190:17 191:7	349:10 350:4,8	19:13 195:23	Tecum 6:6
43:7 45:7	191:11,14	352:10 356:13	196:8 197:8	tee 87:7
54:14,17,22	193:21 194:9	356:17,19	talk 10:16 13:16	television 64:17
55:6 56:15,23	194:17,18	357:2,11,21,24	20:1,4 28:11	tell 16:16 35:17
57:4,5,14,16	196:24 197:3	359:14,22	43:4 44:19	44:11 59:2,4
57:23 58:2,10	199:6 200:23	361:6,12 362:5	65:6 87:8	59:10,13 70:7

72:24 78:19,23	169:5 306:24	366:7 374:6	294:9 461:11	356:11 366:8
93:18 118:21	415:24 417:21	402:4,18	Thanks 210:19	377:1 378:19
143:8 182:12	418:5,8 420:9	403:20,23	388:3 483:19	399:13,22
212:1 227:24	452:17 473:2,3	447:16 463:20	theirs 278:14	400:12 401:4,6
234:13 278:1	476:7	465:1 468:12	theories 30:17	401:12 404:15
313:4 344:5	tested 119:7	468:20 485:8	32:12	404:24 405:5
352:12 375:12	122:11 123:12	testing 113:18	theory 201:5,18	405:12 409:12
379:22 399:3	123:19,22	114:12,21,23	202:20 203:21	438:4 439:13
402:1,1,5	125:4 126:3,6	119:16 120:4	therapy 273:20	443:5
420:13 435:14	128:1 129:23	120:11 121:20	369:3	think 13:4 26:5
471:14 479:19	135:7 143:20	122:6 123:19	thick 319:15	30:20 32:14
telling 131:7	144:15,22	124:1,7,10,20	thing 13:8 31:20	33:12,13,16
172:9 348:14	145:3,13 146:5	127:18,21	59:5 75:13	35:22 50:7
348:18 432:24	147:6,8,8,11	128:22 129:16	103:2,9 120:6	54:2 58:15
TEM 129:3	147:13,20	129:19 130:1	144:3 165:13	59:16 61:13
133:23	148:4 174:9	130:10 131:8	166:19 203:3	69:4 80:1
ten 69:12 79:6	175:18 178:1,9	131:17,22	212:6 233:7	87:10 88:3
210:14,15	374:21 379:2	132:13 134:13	234:10 261:18	109:7 133:6
299:9 300:7	415:14 417:20	134:23 135:2	304:12 316:11	148:14 153:16
316:9 317:1	418:10 448:18	137:12,16	318:2 329:3	154:7,11 155:9
322:3 325:2	448:21 459:7	138:23 140:15	358:16 376:7	157:21 161:12
tenens 46:4	459:21 471:4	142:18,23	400:11,14	173:2 190:12
tenets 288:16	471:17	148:23 174:8	409:8 427:3,16	194:20 195:19
333:17 366:22	testified 9:11	181:16 373:19	things 32:23	196:4 197:19
term 133:6	221:5 385:22	378:22,24	71:9 72:6 77:3	198:17 205:24
344:17	442:15	379:22,24	98:9 108:23	222:20 241:12
terminal 188:21	testify 85:19	380:2 415:23	111:1 114:15	245:24 246:13
termination	87:15 95:13	418:5 448:2,12	127:13 153:20	246:19 261:23
10:3	135:18 401:18	451:18,19	165:18 166:4	262:6 271:12
terms 80:19 86:2	485:5	452:2 459:5,15	166:20 167:3	281:4 283:5
115:14 116:2	testifying 23:12	464:1,5 471:10	170:8 171:6,8	285:2,7 289:2
126:14 134:12	24:17 127:16	471:14	173:12 174:10	300:3 304:11
152:3 190:8	390:17 400:11	testings 130:4	176:6 181:17	316:9 317:6
223:10 226:9	testimony 24:6	374:19	182:8 187:24	318:15 325:4
250:12 274:6	27:4 35:5 57:8	tests 45:16	195:13 200:18	326:4,23 327:4
374:23 446:22	62:22 76:20	117:15 129:1	200:19 205:17	328:17 332:21
452:24 454:7	77:12 80:7	134:22 250:11	210:23 229:5	333:4 337:2
456:12	98:13 121:13	417:8	229:10,24	343:1,21 344:5
Terrific 41:2	122:10 132:17	Texas 1:15,19	248:17 253:12	346:12,13
test 110:9	132:22 139:2,4	3:13 49:13	260:7 273:16	353:3 361:22
114:14 115:9	141:15 142:7	text 99:15	273:23 278:7	362:3,10
115:11,15	147:3 172:1,5	textbooks 63:22	292:6,13 297:6	364:17,24
116:4,20,23	183:10 212:8	Thank 40:9	302:11 303:24	365:2 367:20
121:10 122:6	236:21 257:21	44:17 52:16	306:3 312:24	371:5,6 379:14
140:8 145:19	282:16,21	89:12,16 90:1	313:1 333:5	381:14 384:24
146:24 148:17	296:6 342:21	93:1 225:15,18	336:1 354:23	388:1 389:12

389:16 390:3	235:20 236:17	254:24 265:22	title 295:1 355:4	432:9 433:4
390:13 393:24	236:22 237:10	269:16 285:9	447:21	traced 442:16
399:23 401:11	257:2 267:23	285:12,19,21	today 9:18 10:20	442:17
403:2 422:1	267:24 268:2	300:23 315:7	12:1 13:17	track 191:2
424:20 426:13	282:3,10	315:11 317:2	24:6,17 32:1,2	tract 191:15
443:20 445:2	288:24 311:22	318:3 325:13	42:8 68:2 76:2	192:17,23
445:13 451:1	threshold	326:11 327:8	77:9,19 81:14	193:9 229:7
451:21 459:13	168:11,18,22	332:24 350:3	91:24 93:5	336:18 387:2,8
465:3,16 471:7	183:1	351:12 352:11	130:22 220:10	387:9 436:14
478:16,19,21	tied 193:8 195:3	357:9 361:19	341:19 344:21	436:20 437:15
479:11 483:16	198:4 200:23	362:17 363:4	357:15 358:2	440:22 474:3
thinking 15:9	201:9,9,15,17	364:10 365:19	359:7 375:15	tracts 438:18
152:21 318:6	201:21 202:8	372:19 378:4,9	388:4 389:2	traditionally
thinks 33:16	203:23 204:6	378:20 379:1	442:15 446:4	297:9
132:21	208:13,16	379:18 388:4	447:13 461:6	training 42:16
third 26:19 48:3	till 67:7 95:20	388:10,14	463:5 468:12	transcript 24:4
94:5 101:8	281:23 324:23	399:19 410:5	477:17 482:12	485:7
112:14 233:13	time 9:5,23	422:7,16	482:23 483:1	transcription
258:11 320:18	10:17 26:19	424:24 432:13	483:14	486:5
355:23	27:14 37:18	440:12 444:2,6	Today's 9:4	translocation
third-party	44:2 46:7 47:1	445:18,22	toilet 436:16	430:3,10,20
130:1 137:21	47:6,15,18,22	455:1 461:17	438:3	transmission
Thirty-three	48:6,10 49:22	461:21 470:17	told 45:8 57:24	133:19 419:13
225:5	50:13 52:1,7,9	473:18 475:10	87:5 362:3	451:20
Thompson 2:3	52:13 53:9	484:4 485:8	463:17 480:4	transport
42:2,4,5,12	54:7 59:18	times 65:9 78:8	tool 286:13	227:10
43:22 477:17	61:22,24 66:24	172:6 184:3	top 38:17 167:1	travel 193:22
481:18	72:8 89:18,22	269:12 290:14	332:8	194:4,23
Thompson's	90:6,19 96:5	299:9 300:7	topic 14:12	195:13
42:8	97:20 107:5	334:1 475:9	395:1	traveling 194:10
thought 12:23	108:16 111:23	Time-out 171:24	total 75:13	treat 12:21
15:24 16:6	112:8 114:13	171:24	97:21 108:17	47:17 48:23
97:23 135:8	115:6 123:9	timing 211:23	259:2 296:11	272:15
281:24 285:8	129:14 139:7	212:16	358:4,21	treated 47:22
321:8 330:6	139:12 143:11	Tinto 471:16,23	totality 100:8	48:1 156:1
342:18,21	155:4 172:23	Tired 380:17	456:1	treating 47:1,3
393:22 424:4	186:2,3 188:20	tissue 212:20,21	touched 446:23	52:2,9,14
425:1,5 455:22	188:24 189:13	215:2 407:17	tough 472:21	73:11 155:24
480:4	190:1,14,14	409:16 433:8	toxic 167:6	187:4
thousand	203:11 212:5	434:12 436:22	169:22	treatment 56:6
215:22 305:6	213:12,16	440:7,11,18	toxicity 179:23	274:10
thousands 408:5	218:5,11,20	441:1,5,7	toxicology	treatments
three 10:2 47:8	219:19 237:13	tissues 434:14	384:24	350:13 351:24
69:4 78:8	243:20 245:19	435:16,18	toxin 325:21	tremolite 117:10
101:7 227:1	247:9 252:12	437:3	toxins 166:21	117:11,11,12
234:16 235:6	252:21 253:2	Titanium 7:13	trace 183:11	117:12,13,17

117:18,24 118:1,7,8,21 trend 331:8 trial 28:13 tricky 38:20 tried 108:15 306:5 trouble 51:3 true 38:10 41:22 42:2 55:21 57:6 58:7 59:11,24 60:6 62:13 63:10,19 63:22 64:2 82:22 116:5 125:23 130:24 133:16,19,24 134:11 135:4 139:19,22 146:24 167:21 182:1 188:15 191:2,24 194:5 201:5,18 202:22 216:23 217:8,15 224:6 225:24 227:6 234:4 236:10 244:5,8,14 252:4 265:17 266:18 271:8 273:20 282:6 283:21 336:21 343:15 352:10 355:1,9 357:3 371:18 469:16 469:19 truly 347:15 truth 485:5,5,6 truthful 353:3 353:14 try 10:16 31:24 117:5 220:4 260:16 333:3 344:8 trying 14:10 29:4 38:19	53:14 62:21 130:21 199:4 211:4 212:15 236:14 246:14 277:12 464:9 tubal 197:24 202:22 tube 8:7 272:8 382:16 tubes 193:7,8 195:3,3 198:4 200:23 201:9,9 201:15,17,21 202:8 203:23 204:6 208:12 208:16 440:13 442:12,19 456:24 473:7 473:19 TUCKER 3:20 tumors 21:3 241:2,3,11,12 242:8 turn 143:14 226:13 371:1 385:20 394:12 394:16 418:22 448:10 449:19 450:6 455:10 turned 96:13 172:22 TV 64:1 tweaks 97:23 tweeted 462:18 Twenty-four 60:1 twice 170:22 189:1 twine 237:18 two 7:6 45:4 49:2 101:7 110:13 140:22 176:10 191:6 205:16 215:22 227:1 229:9 236:22 239:6	239:14 242:6 251:5,7 257:1 258:21 261:17 267:22 268:1 277:18 283:2,6 292:19 305:6 323:22 381:15 446:4,24 450:24 465:19 467:11,12 477:18,19 two-year 44:10 type 36:21 38:20 39:6 69:17,19 97:4 150:14,20 151:2,5 238:6 239:4 242:9 248:4 270:7 409:16 432:4 451:18 473:23 479:23 typed 37:8 38:6 38:9 69:22 97:8 types 116:15 150:17 241:3,7 412:9 416:19 417:13 typist 53:18 97:14 typos 98:1 T-a-h-e-r 90:16 U ubiquitous 417:13 474:14 474:22 475:5,7 Uh-huh 55:24 99:17 101:10 199:18,21 210:17 211:2 250:1 339:15 392:2 414:8 ultimately 397:15 456:14 unaware 77:10	uncertain 276:19 uncertainty 274:6,11 unclear 137:24 undergone 188:11 underlying 40:6 understand 10:19,23 14:15 27:4,6 34:4 35:6 38:2 44:22 48:15 49:18 53:15 61:13 62:21,21 76:2 82:11 83:15 86:18 89:1,2 92:12 95:24 105:22 115:11 116:18 127:12 130:22 131:12 138:3,4 139:17 144:14 144:18,19 146:10 152:10 167:9 182:13 184:17 193:15 199:13 203:11 248:22 249:13 250:17,20 251:10,14 252:10 269:19 282:15 285:23 286:21 298:7 300:4 349:18 369:20 371:16 371:22 376:16 377:12 380:18 384:15,20 402:21 404:1 406:10,12,13 406:16 416:18 419:17 420:5 433:23 442:14 463:24 466:7 469:4	understandably 334:8 understanding 16:13,17,24 17:14,20,23 20:17,20 24:18 25:11 27:15 34:10 43:21 70:11 80:18 81:2,13 89:4 96:22 167:10 168:1 169:12 180:3 181:23 187:10 222:18 262:15 269:4 301:11 317:19 318:11 328:16 361:14 375:9 466:11 468:21 469:2 understood 11:3 24:11 39:13 220:10 343:11 464:24 undertake 251:3 312:16 undertaken 349:10 undertook 349:15,19 underwear 206:3 335:8 unethical 28:8 28:12,17 unexposed 259:4 unfortunately 310:7 United 1:1 124:19 449:2 universally 221:19 222:11 223:5 459:5 unpublished 235:21 236:17 untoward 40:19
--	--	--	--	---

untruthful 353:9	267:16 268:5,6 274:2,14	299:4 337:16	379:14,15,23	walking 195:18
update 53:11	286:12,17,19	usually 13:9	versa 243:1	436:17 474:17
234:22 302:5	289:4,9 290:15	34:13 241:16	version 8:9	want 10:1 13:8
362:4	290:24 291:4	343:6 358:15	117:19 118:2	13:10 39:3
updated 52:21	292:14,20	uterus 439:23	172:24 258:4	40:20 44:19
53:13 54:4	293:21 294:24	440:8,19,23	272:10 275:19	58:15,16 76:1
72:8 279:13	295:18 298:9	441:3,8,15	versus 21:1	76:3 77:22
282:18	301:14 302:1,2	442:9,19	153:17 163:2	78:6 85:6,12
Updates 279:1	304:21 308:3	V	189:7 247:24	86:17,21 87:6
upper 263:1	308:17 309:19	V 4:6	271:3 328:1	119:11 129:15
437:14	309:23 310:1	vacation 47:9	vice 243:1	137:11 138:19
UpToDate 6:7	310:10 313:21	vagina 192:12	vicinity 423:4	138:21 176:7
12:11,18 13:2	315:15,17	192:22 193:5,9	VIDEOGRAP...	192:15 198:14
13:7,11 31:22	317:19 318:16	193:22 194:4	9:2 89:17,21	203:2,3,10,11
33:1,8,13,19	318:20 319:4	194:10,19	139:6,10	208:21 212:5
34:1,4,7,16	320:19,21	195:16 230:3,8	213:11,15	224:18,24
106:3 269:21	322:8,10 323:1	232:6 387:11	252:20,24	225:13,20
up-to-date 366:4	323:10,19	388:2 437:14	315:6,10 378:3	230:23 231:6
urban 476:3,16	324:23 325:14	441:2,5 443:1	378:7 388:9,13	244:12 245:6
usage 7:8 472:12	328:12,23	443:14 456:23	444:1,5 445:17	251:14 253:7
use 7:5,18,21 8:4	330:5,7 331:3	vaginal 387:2,8	445:21 461:16	263:22 296:19
29:24 32:3	332:3,5,23	387:9,10 442:2	461:20 484:2	299:13,13
37:14 45:7	334:6,21	442:18	Videotaped 1:12	305:5 332:20
56:2,24 59:3	337:23 345:1,7	vague 137:24	6:5	361:24 364:13
59:11 89:8	348:4,15,18,19	validity 106:9	view 19:11	364:14 370:23
106:5,20,23	350:9 352:10	variable 327:4	121:5 164:9	371:22 377:12
107:1,22	356:13,15	various 114:13	171:5 209:12	383:6 390:14
108:16,16	357:2,12 361:6	114:13 116:15	362:20	390:23 397:17
110:17 126:23	361:12 368:6	241:14 361:21	viewing 393:17	397:23 424:24
133:23 142:1,4	400:18,23	418:5	vintage 136:18	427:1 438:1
153:10 162:18	401:13 404:21	varying 169:6	virtually 391:14	443:23 444:9
170:19 173:9	405:2 406:3	240:23 242:8	virus 166:23	467:5 472:12
181:10 185:16	416:21 420:23	vast 440:2	Vitae 6:13	wanted 51:6
189:8 203:23	433:8 434:13	verbal 85:9	vital 434:3	60:21 61:21
203:24,24	435:17 436:17	verbatim 485:7	vitamin 433:21	66:4 71:5
204:18 205:5	450:13 472:5	verification	vitro 14:14	220:2 265:4
209:13 234:20	473:11,12	262:12	106:8 220:5	295:23 313:1,1
237:6,13 241:5	user 318:10	verify 173:16	268:16 269:1	358:19
245:9 248:18	users 297:9	263:4 427:2	384:6	Ware 328:9
249:9 251:22	317:2	Vermillion 46:2	vivo 269:1 384:7	warehouses
251:22 253:15	uses 67:13 108:1	46:8,21 47:15	volume 7:12	135:12
253:22 264:10	109:11 163:3	47:19 48:16,19	361:18 430:14	warn 411:5
265:17,21,22	164:22 181:10	48:20 50:6,9	431:12,14,19	Washington 4:4
265:22,22	190:17 205:19	50:18 354:7	454:20	wasn't 33:7
266:18 267:6	206:15 298:10	Vermont 135:22	W	56:20 57:20
				59:18 118:5

150:18 152:21	90:13 279:13	211:15 213:8	50:20 57:3	90:2 93:4
153:9 212:23	282:19	225:12 238:21	62:12 79:4	102:22 110:16
215:4 236:12	weigh 246:22	239:14,21	83:18 86:6	113:13 114:18
242:13 248:7	weight 137:19	244:24 247:14	88:9 92:21	120:3 121:19
266:11 267:12	138:9,14,21	321:12 368:2	112:3,7,10	128:18 129:10
280:9 293:2	197:1,9,14	423:19 473:1,2	120:16 126:15	129:12 132:6
322:18 346:6	254:18 268:9	we're 13:16 20:4	128:13 132:9	137:10 139:14
357:14 363:5	268:18 269:19	27:5 41:12,15	136:24 138:1	141:15 146:10
438:10 444:13	269:20 270:2	54:2 62:20	141:8,12,24	149:15,18
waste 212:5	275:2 277:7	66:8 67:22	143:15 144:5	156:21 167:10
424:24	278:3 281:18	87:3,22,24	174:1 202:17	170:13 172:9
wasting 269:15	290:5 334:11	95:22 127:5	203:5 207:7,11	178:13 198:16
300:23	382:21 383:3	134:2 149:8	208:6 210:17	199:14 213:20
watch 326:10	weighted 264:3	162:9 229:9	215:21 216:2,9	216:6,12
water 421:14	270:6	236:14 237:14	225:5 233:5	230:12 231:24
422:7,16 450:4	weighting	241:9 276:3	238:15 240:5	234:3 236:15
way 24:13 71:10	126:14	296:18 300:23	247:18 287:18	243:4 253:4
149:17 153:3	WEIL 2:18 3:2	321:9 322:6	294:1 300:9,16	267:20 277:22
166:5,14 195:2	Weiss 320:23	343:12 349:2	320:1,4,8	280:11 300:24
204:4 217:11	welcome 18:19	359:6 424:18	346:3,6 349:5	301:7,8 315:13
220:5 255:7	26:21 86:1	483:24	383:17 386:3	340:4 351:2,5
267:19 325:4	89:24	we've 25:14	386:13 389:18	357:17 370:23
326:2 327:14	well-known	31:15 35:19	389:22 391:24	378:11 380:6
337:9,11	352:9	36:4 66:19	392:7 394:13	388:4,17 409:9
366:13,15	Welt 293:2	67:19,20 79:6	397:18 424:7	418:17 423:19
401:16,16	went 45:19	88:17 97:4,16	425:10 426:19	432:18 444:8
443:3 455:8	48:21 64:1	139:4 140:22	430:7 438:13	446:3 454:6,24
457:4,6 459:9	81:3 155:15	158:1 210:8	460:12,24	455:11 461:11
Wayne 480:2,7	200:7 229:14	224:13 232:19	461:3 483:23	461:24 468:6
ways 381:15	334:3	272:5 294:17	witnesses 93:15	470:23 472:20
weak 222:22	Wera 8:5	358:1	401:20	475:21 482:10
223:12 226:9	weren't 41:8	when's 66:17	witness's 76:19	484:4 485:5
227:11,22	54:10 80:3	WHI 317:10	Wolf 1:13 5:1,6	486:12
weaknesses	204:6 257:12	white 297:1,10	6:1,5,15 7:1	Wolfson 401:19
270:9	287:13 317:7	Whites 8:12	8:1,18 9:3,8,14	435:14 456:15
website 128:20	405:12	292:11,16	11:11 18:16	Wolf's 107:16
272:7 351:14	West 2:14	Wikipedia	26:21 27:6	147:2
359:10,14,18	we'll 10:16 11:6	104:18,20	36:22 37:15	woman 107:12
362:4 365:20	11:9 12:6	105:2,9	38:2,4 39:12	108:1,19,21
446:5 447:22	27:24 35:12	Wilson 420:13	40:1 41:4,19	109:10 162:24
449:12	37:7,10 40:6	wiping 195:17	45:24 57:4	163:1 164:22
websites 361:3	41:3 85:7	withdraw 203:9	62:20 80:1,9	171:10 181:3
week 49:7	86:15 87:7	witness 9:7,9	83:8,13,17	181:12 189:13
170:22	88:5,16 92:6	10:8,10 17:5	84:22 85:22,23	193:6 195:1
weekly 190:18	123:8 156:21	18:20 19:4	86:4 88:15	201:15 205:12
weeks 47:8	198:15 211:4	23:22 44:24	89:3,12,24	205:19 206:1,7

208:2,23	352:22,23,24	343:24 349:12	writing 72:6	320:13 330:19
209:12 460:19	353:4,17	349:20 357:17	96:15 104:2,17	347:11 388:7
464:10 473:24	354:20 387:1,7	358:7,21 359:2	160:12 245:17	392:14 394:18
woman's 64:23	387:8,9,12	360:3 362:13	246:6 353:17	422:13 424:22
166:15 167:19	400:18 401:1,3	363:10 382:5	354:4,10	427:18 429:21
169:17 174:15	401:13,23	382:11 386:3	389:10	442:7 450:5
176:4,9 180:9	404:21 405:2	395:16,24	written 203:6	459:12 461:13
189:8 190:13	405:19,20,21	396:11 463:11	386:12 446:18	year 31:19 36:12
204:13 241:6	406:2,11 408:5	481:5	wrong 30:10	47:8 49:5
439:22	408:13 411:5	worked 47:19	148:9 239:10	106:14 306:12
women 42:22	420:23 422:6	63:8 480:2	285:4 319:22	306:21,21,24
45:15 56:24,24	422:15 423:3,7	working 12:23	wrongful 10:2	308:10 314:21
159:6,17 161:8	423:15 426:5	43:9 45:24	wrote 98:11,18	325:1 332:11
161:12,15	428:15 429:1	46:1 49:6 50:1	100:2,19	362:14 401:19
163:23 164:2,8	433:8,9 434:13	50:6 51:16	171:22 172:11	478:6,21
164:21 170:19	434:14 435:16	52:7 53:10	228:3 236:12	479:12
196:7 197:7,24	435:18 437:3	159:2 169:15	351:3 354:16	years 10:2 20:23
200:22 202:7	440:2 441:10	227:9 352:14	469:23	45:4 48:2 55:1
202:22 203:16	445:2 473:17	354:6 364:20	Wu 8:13 234:17	55:11 59:22
203:23 209:3	474:16	376:18 386:7	235:9 238:12	60:1,2 62:22
209:11 227:11	women's 55:10	426:1 428:20	238:15,21	63:10,11 64:7
234:20 235:1	63:9,13,18,24	429:8 430:15	239:16 292:3,7	108:16 148:23
238:8 254:23	236:23 237:1	430:18 455:12	292:13,23	170:23 186:10
256:9,13	257:8 265:24	464:10 478:23	293:19,22	190:18 199:7
259:21,24	321:9,12 324:2	479:6	294:2,17,21	228:10 280:5
292:10,15,24	324:13,18	works 97:13	295:1 296:4	283:2,6 316:14
293:20 294:22	353:5,13	166:13 169:12	297:7 312:9,13	317:12 318:18
295:24 296:11	364:21 365:3	workshop 385:7	329:20,21	322:3 324:5,20
296:23 297:1,8	366:1 438:18	work-product	330:1	324:23 325:2,2
297:10,18,21	word 61:9 71:2	84:7	Wu's 239:12	325:3,18,19
297:22 298:1	464:2	world 341:10		326:6,18
298:18 301:13	wording 156:18	379:21	X	330:10,21
301:17 302:1	words 99:24	worrisome	XRD 115:9,15	331:1,3,9,21
302:23 303:2,5	102:15 455:16	181:20,23	451:20	366:1 379:11
304:3 315:17	work 10:4 30:13	worry 58:1	Y	399:5 439:22
316:18,19,19	39:21 41:22	wouldn't 160:15	yeah 37:6 44:17	477:19 480:15
316:20,22	43:1,3 44:24	237:2,3 244:12	44:21 50:15	York 3:4,4
317:11,17,20	49:23 50:4,4	329:19,24	68:15 113:6,10	young 315:16
318:23 319:4	50:10,13,20	375:2 387:6	143:22 179:16	316:1,23
320:21 321:3,4	61:16,19 73:10	390:14 460:22	225:15 230:18	318:13,17
321:5,14,16	99:5 121:24	write 64:8 98:5	238:17,18	320:20
322:8,9,23	122:1,7 166:4	100:10 142:24	239:14 242:18	
323:9,19	166:21,22	353:4,12	263:2 269:23	Z
325:15 342:21	167:11,18	354:11 360:1	273:18 275:12	zero 325:3
343:1,5 345:7	207:11 220:15	361:24 362:8	319:9,24	\$
348:4 352:17	220:20 272:13	385:23		

\$600 38:5 358:9	198:16,21	16-2738 1:4	35:1 105:17	2008 281:23
0	224:4 330:18	17 2:19 8:4	139:11 303:20	2009 127:21
0.005 307:2	11th 351:2,8	221:17 247:15	308:20 375:13	128:1 129:20
07962 3:17	11:18 139:7,8	247:16	375:16,19	2009-2010
08542-3792 2:20	11:27 139:9,12	1700 295:24	448:11	128:23 471:3
1	1100 3:21	296:4,11	2B 284:18	201 2:19
1 6:4 7:14 11:12	12 6:7 7:7 69:12	18 8:7 70:12	2.5 347:10	2010 127:21
11:15 38:21	71:21 79:11	272:2,6 275:16	2:21 252:21,22	128:1 129:20
39:17 67:20	213:17,21	449:12,20	2:26 252:23	187:23 222:20
68:3 283:16	316:8 332:11	450:7,7	253:2	224:6,24 228:3
330:9,22 332:1	380:13 384:3,4	19 2:9 8:10	20 8:14 74:12	245:10,22
369:10,15,16	394:17 449:19	53:23,23	76:16 78:3	246:9 319:23
369:22	12:44 213:12,13	294:11,13,17	81:4 97:21	320:7 430:14
1st 49:21 51:4	12:45 210:9	302:8	199:7 316:14	454:21 455:13
479:7,9	128 6:17 296:2,7	19103-6996 3:8	317:1,12	455:16 469:20
1.2 287:24 369:1	296:8,12	1970s 120:4,12	318:17 324:5	470:4
371:18,19	13 7:11 72:11	121:11,21	324:19,19,23	2012 425:20
1.25 259:6 262:1	74:10,18 77:8	123:14,23	325:3,18 326:6	428:5 430:16
262:8	78:4 79:3	124:3,11	326:18 331:5	431:5,15,20
1.3 368:10,21	80:10 224:15	126:21 127:18	350:19,20	457:10
369:1,14 370:5	225:6,11,17	130:11	352:21 354:9	2013 451:3
370:21 371:13	319:13 424:3,8	1971 215:22	357:10 371:7	2014 7:14 48:5
371:20	424:10 449:20	1975 120:8	375:14,16,19	228:22 229:11
1.4 368:10,21	454:22	1976 143:2,5	380:7,14,15	232:2 234:1
369:1 370:5,21	14 7:14 232:20	144:22 145:6	414:3,10,11,20	237:2 303:7
371:13	233:1 238:21	145:19 146:5	446:5 462:2	304:2,17,18
1.5 347:9	239:22 275:1	146:24 147:20	486:16	307:9 308:2,6
1.6 287:24	275:14,17	148:10 321:6	20-some-odd	308:23 309:23
1:41 213:14,16	1413 306:18	198 7:4	74:9	310:1,9,13
10 6:19 156:22	1414 239:2,6,9	1982 321:7	20-60 371:4	311:5,15,24
157:1,17,19	303:20	323:1	200,000 256:9	313:19,20
158:2 193:16	1416 310:19,20	1989 320:23	256:15,18	314:9 329:12
224:4 340:17	1490 2:14	1990s 134:14,17	259:20,23	329:18 444:22
369:1 424:2	15 7:16 81:4	1991 141:19	371:14	451:5
425:19 427:3,5	186:9 224:14	142:3,8	2000 3:8 451:1,5	2015 44:8 45:23
427:11 428:6	225:9,10	1992 17:16	2000s 451:1	46:1 67:7
429:20 431:2	238:22 302:10	1994 385:7	20004-1454 4:4	235:9 351:3,8
473:8	326:6,18	1995 17:17	2003 451:2,3	352:3,8 354:17
10:21 89:18,19	334:14 367:20	481:15	2005 67:1	356:12 357:1
10:33 89:20,22	1510 3:12	1996 17:19	2006 31:11	2016 53:6
100 6:16 85:16	157 6:19	213:22	455:2 469:23	197:20 198:12
320:6,8	16 7:21 36:3	2	470:10	198:16 200:8
10153-0119 3:4	95:6 101:5	2 5:3 6:7 12:7,8	2007 207:4,24	207:12,18
11 6:4 7:4	245:1,2 450:6	12:16 13:19	281:23 282:9	235:9,9 239:17
	16th 93:11 94:21	33:2,8 34:8	282:14 287:13	240:8,9 278:11
	96:17		287:17 469:23	280:8 329:22

451:4,15	323:10,19	334 2:5	44 450:3	6 6:13 52:21,23
2017 37:3 38:5	256 157:5	338-1100 2:15	44113-7213 3:22	53:15,20 258:2
41:22 44:7	158:24 425:17	339 198:14	446 5:9	258:4 290:21
49:19 52:22	425:24 428:12	200:20	45 450:3,8	6:16 445:20,22
53:16 236:6	26 6:14,16	34 308:23	46 245:7 262:19	6:36 461:17,18
2018 36:4 49:21	267-0058 3:18	309:17,21	262:22	6:44 461:19,21
51:1,4,15	269-2343 2:5	34.4 309:11,17	461 5:10	60 52:4 111:14
53:17,20 93:11	272 8:7	309:23	463-2400 4:4	111:18,23
94:21 95:6	2738 1:7	35 6:11 330:10	47 373:13,14	121:6 124:22
96:18 235:2	274 426:12	331:2,5	415:10,15	125:4,6,9,20
278:13 279:14	277 455:10	350 3:17 8:14	416:24 418:23	126:2,6,11
280:9 479:10	28 113:14 114:2	353 8:17	420:12,14	131:7,10 371:8
479:14	114:7,10,21	36 6:12 308:24	470 5:11	371:10
2019 1:9 5:2 6:2	120:20,24	321:7,21	482 5:12,13	60s 438:8
7:2 8:2 9:4	132:8,11	322:24	485 5:15	600 358:22
12:12 53:22	138:10 139:22	36.5 310:9	486 5:16	609 2:20
485:19	140:2,5,21	36104 2:5	487 5:17	61 321:7,21
202 4:4	374:6	388 5:8	488 5:18	322:24
21 8:17 273:11	28-page 70:21	391-0197 3:13	<hr/> 5 <hr/>	619 2:15
274:9 275:1,11	71:1	<hr/> 4 <hr/>	5 6:12 17:13	66 6:14
275:14,15	280 426:10,11	4 6:11 8:15	25:16 36:18	696-3675 3:22
353:20,24	426:20 428:4	35:12,13,19	38:3,10,13,21	<hr/> 7 <hr/>
354:15 357:10	429:5,12,17	36:5 351:1	39:17 40:4	7 1:9 5:2 6:2,14
446:5 462:2	294 8:10	378:8 383:2,7	41:20 383:2,7	7:2 8:2 66:12
21st 279:13	<hr/> 3 <hr/>	383:8 391:5	383:8	66:13,19 96:17
212 3:4	3 6:8 31:8,12	394:11,17	5th 12:12	97:5,17 98:6,7
213 7:7	33:3 240:2	399:9	5-milligram	98:14 274:9
215 3:9	253:1 270:12	4th 1:15 35:22	333:1	7th 9:4
216 3:22	273:11	52:22 53:20	5:02 388:10,11	7:03 484:5,7
218 2:4	3:24 315:7,8	4:40 378:4,5	5:06 388:12,14	70s 378:24 438:9
22 8:19 427:22	3:40 315:9,11	4:52 378:6,9	5:51 444:2,3	71 216:8
428:3	30 59:22 97:21	40 325:18	5:52 444:4,6	720-1288 2:10
224 7:11	199:7 228:10	347:12 371:5	5:54 445:18,19	7200 332:3,4
23 215:11,14	309:15 318:17	40s 316:20	50 48:4,7	767 3:3
216:22 217:3	321:6 366:1	41 379:3 450:2,8	50s 316:20	78701 3:13
233 7:14	371:5	459:6,14 460:5	500 1:14	<hr/> 8 <hr/>
238 7:16	30s 21:21	460:8,16,20	501 2:14	8 6:16 99:14
24 60:2 62:22	30-year 317:2	411 226:13	51.5 310:13	100:19,21,22
63:10 64:7	30-50 290:22	42 253:8,10	512 3:13	102:12 255:15
214:21 215:3,8	305 319:13,20	309:15 379:3	52 6:13	260:5 261:13
216:17	320:5	450:3 459:6,14	55 321:6	331:5 371:3
245 7:21	31 6:8	460:6,9,20	55-year-old	485:19
247 8:4	310-8468 3:4	427 8:19	318:9	80 315:17 319:3
25 315:18 319:5	33 225:1,21	429 259:2	<hr/> 6 <hr/>	320:21 321:15
320:22 321:15	226:8	43 450:3		
322:9,11				

322:8				
816 3:12				
83 358:6,22				
<hr/>				
9				
<hr/>				
9 5:4,7 6:17				
112:13 128:15				
128:19 129:5,5				
129:7,10,15				
447:20 448:11				
470:22,24				
471:1,18				
9:08 1:16 9:5				
90s 16:14 378:24				
90-plus 411:18				
91 374:7				
92101 2:15				
92660 2:10				
93 7:12 454:21				
943 259:3				
949 2:10				
950 3:21				
96 216:12				
973 3:18				
975 4:3				
986-1104 2:20				
988-2706 3:9				
99 259:8				

Exhibit 15

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON
(LHG)
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION

MDL NO. 16-2738 (FLW)

THIS DOCUMENT RELATES TO ALL CASES

RULE 26 EXPERT REPORT OF
SARAH E. KANE, MD

Date: November 15, 2018



Sarah E. Kane, MD

I. BACKGROUND:

I am certified by the American Board of Pathology in Anatomic Pathology, Clinical Pathology and Cytopathology. I received my medical degree from The Ohio State University College of Medicine in Columbus, Ohio. I completed my residency in Anatomic and Clinical Pathology at Massachusetts General Hospital, a Harvard Medical School teaching hospital in Boston, Massachusetts. Following my residency, I completed a two-year gynecologic and cytology fellowship as the Robert E. Scully Fellow in Pathology at Massachusetts General Hospital, named after Dr. Robert Scully, who was a giant in the field of gynecologic pathology. This fellowship was focused on gynecologic pathology, perinatal pathology, and cytopathology. I studied the causes and mechanisms of disease as part of my training, and studied gynecologic cancer and disease in depth during my fellowship training. To this day, I routinely follow the gynecologic pathology literature as part of my regular practice.

I am currently a full partner in a private practice group, Commonwealth Pathology Partners PC. I have staff privileges at Massachusetts General Hospital, North Shore Medical Center (consisting of Salem Hospital in Salem, MA and Union Hospital in Lynn, MA) and Newton-Wellesley Hospital. I was hired by Commonwealth Pathology Partners PC to be the group's gynecologic pathology expert. Although all of the anatomic pathologists in our group practice general anatomic pathology, our group employs fellowship-trained pathologists in many subspecialty areas of pathology. This means that I see the majority of gynecologic surgical pathology specimens from my hospital sites, and if another pathologist needs an opinion on a gynecologic case, I will review it. I also presently serve as the autopsy director at North Shore Medical Center. I regularly attend and participate in numerous multidisciplinary conferences at Massachusetts General Hospital at the Cancer Center site in Danvers, MA.

Before entering private practice, I was a staff pathologist and Instructor of Pathology at Beth Israel Deaconess Medical Center (BIDMC), another Harvard Medical School teaching hospital. During my time at BIDMC, I performed specialty sign-out in gynecologic pathology, perinatal pathology and cytology. I was also served as the Associate Director of the Cytopathology Fellowship Program at BIDMC, served on numerous pathology department committees, and taught several courses at Harvard Medical School before I was recruited for my current position. My curriculum vitae is attached as Exhibit A. It further details these positions and the remainder of my work experience in this field. Exhibit B details the references cited in this report, as well as other materials and data I considered.

I have been asked to provide an expert report regarding my opinions on the question of general causality in the case of talcum powder product use and ovarian cancer. All of my opinions stated below are held to a reasonable degree of medical and scientific certainty. I reserve the right to modify or change my opinion based on further documents or information that may be provided to me in the future.

A pathologist is a physician who has completed medical school and a post-graduate residency in pathology (either clinical pathology, anatomic pathology, or both). Like me, many pathologists go on to complete fellowships following their education and residency.

Pathology is the study of disease; pathologists spend much of their time both in training and in daily practice studying the causes and presentations of disease. The years of medical training are of critical importance in daily practice; pathologists must make clinical assessments, based in part on medical and epidemiologic knowledge, about identification of causes, risk factors, clinical sequelae, morphologic, and genetic features of disease.

In order to produce accurate diagnoses, pathologists must be knowledgeable about the medical, scientific, and epidemiologic evidence base. A knowledge of advancements in technologies applied to tissue samples must be continuously maintained. This involves not only maintaining current knowledge of the pathology literature, but also of the literature in various other fields such as oncology and other fields relevant to our practice.

One of the tools used in the process of identifying talc particles in tissue is polarized light microscopy. Anatomic pathologists routinely use polarized light microscopy in clinical practice. As an example, one might use polarized light microscopy to find foreign material and explain an inflammatory reaction. The most common application in my practice is for identifying calcium oxalate crystals in breast biopsies done for radiologically identified calcifications. I estimate I use polarized light microscopy for this purpose about twice a month.

In anatomic pathology, the pathologist not only needs to be aware of the numerous possible diagnoses, but also of the causes of diseases one may encounter in any given organ system. Coming to a diagnosis requires knowledge of the medical, scientific, and epidemiologic literature. Pathologists must be proficient in the current literature that informs and supports their conclusions.

Ultimately, a pathologist's diagnosis must make biological sense and must be supported by the weight of the available medical and scientific information. Not only must a particular case match the morphological characteristics of the diagnosis being made, but it must fit the clinical presentation, the patient history, and it must be consistent with what is known about the disease, including what is known about disease causation. These are the same medical and scientific information resources that I rely on for my opinions in this report.

Thus, the work that I've done in this report is similar to what I do in my daily practice. My clinical practice requires ongoing familiarity with the same medical evidence that I have considered here.

Ovarian cancer has an incidence rate of 11.8 per 100,000, and thus is relatively rare (Torre 2018). At my current private practice, I am the primary pathologist on approximately 6,000 cases annually. This includes both surgical pathology and cytopathology cases. I would be diagnosing, ruling out, or looking for ovarian cancer or metastatic ovarian cancer (among other diseases), in approximately 2000 cases a year as a rough estimate. Of those, I estimate that I diagnose about 30 cases per year as ovarian tumors. Academic teaching hospitals generally tend to have a higher volume of ovarian tumor cases due to their large referral bases. While I was a staff pathologist at Beth Israel Deaconess Medical Center, the pathology department implemented a subspecialty sign-out schedule in 2010. In my last two years there,

I signed out predominantly gynecologic surgical pathology in addition to cytopathology (in prior years the department had a general surgical pathology schedule, which meant all types of cases went to each anatomic pathologist regardless of subspecialty fellowship training). During that time, I estimate I signed out about 500 ovarian tumor cases per year. Similarly, while I was a fellow at Massachusetts General Hospital from 2005-2007, I independently signed out gynecologic surgical pathology and estimate I signed out approximately 500 ovarian tumor cases per year. As a resident in anatomic pathology at Massachusetts General Hospital, I was exposed to hundreds of ovarian tumor cases both during my clinical case work and didactic sessions.

Of note, during my time at Massachusetts General Hospital, both Drs. Robert Scully and Debra Bell were still working in the Department of Pathology. Dr. Scully was a co-author on Dr. Cramer's first paper on talc and ovarian cancer in 1982, and Dr. Bell was a co-author on Drs. Harlow and Cramer's 1992 paper on talc and ovarian cancer. Dr. Bell's tenure as Cytopathology Director also overlapped with my time there. This meant that I spent significant time with Dr. Bell during my residency and fellowship. I was the primary author of a paper on ovarian serous borderline tumors in 2006, with Dr. Bell serving as a co-author. Dr. Scully, known as a giant in gynecologic pathology, was semi-retired by the time I started my pathology residency in 2001. However, he was at the hospital nearly every day and all of the gynecologic pathologists would still show him cases on a consult basis. Dr. Robert Young, the director of my fellowship program, was a Scully protege and continued his consulting practice. It is because of my training at Massachusetts General Hospital and my interactions with both Drs. Scully and Bell that I first became aware of their work on talc and ovarian cancer. Since then, I have maintained a professional interest in and have continued to monitor developments in the science regarding talcum powder exposure and ovarian cancer, and it has been the subject of professional discussions pre-dating this litigation.

My billing rate is \$500 per hour. I have previously testified in one matter, a deposition for the case of Julie Lagadimas, as Personal Rep. of the Estate of Dawn M. O'Toole v. R.J. Reynolds Tobacco Co., et al; Norfolk Super. Ct. Case No. 1582-CV-01474.

II. GENERAL CAUSATION OPINIONS:

Based on assessing and weighing the totality of the evidence, and following the methodology set forth below, I hold the following opinions to a reasonable degree of scientific and medical certainty:

1. Talcum powder products and their constituent minerals can reach the ovaries through migration up the genital tract from the perineum to the fallopian tubes and ovaries. There is also evidence that these products can be transported through the lymphatic system (Cramer 2007). Another biologically plausible pathway is inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011).

2. Once reaching the ovaries, talcum powder products can cause chronic inflammation, can increase oxidative stress, and can reduce immune response. These are biologically plausible and likely mechanisms for ovarian cancer development and progression.

3. There are chemical similarities between asbestos and talc and there are striking pathological similarities between invasive serous ovarian cancer and mesothelioma.

4. There is evidence that talcum powder products manufactured by Johnson & Johnson (Johnson's Baby Powder and Shower to Shower) have contained and continue to contain asbestos, talc containing asbestiform fibers (fibrous talc), and heavy metals such as cobalt, nickel, and chromium. Other than cobalt, which has been identified as a "possible" carcinogen by the International Agency for Research on Cancer (IARC), all of these constituents have been identified as known carcinogens by IARC (IARC 1987, IARC 2012).

5. For purposes of my opinions, I have reviewed and relied upon Dr. Crowley's report regarding the fragrance chemical constituents in Johnson & Johnson talcum powder products (Crowley Report), as well as testing reports and analysis which include, Dr. Blount (Blount Report), Dr. Longo and Dr. Mark Rigler (Longo et al. Report), as well as the corporate testimonies of John Hopkins and Julie Pier. The presence of these constituents as part of talcum powder products provides additional evidence of biological plausibility for causation regarding talc and ovarian cancer.

My opinions and conclusions are supported by epidemiologic studies showing an increased risk of ovarian cancer in women who used talcum powder products for perineal dusting, animal and in vitro studies, cellular biology studies, and pathological evidence which provides a highly biologically plausible mechanism for talc's carcinogenicity. Based on the totality of evidence, it is my opinion to a reasonable degree of scientific and medical certainty, that perineal exposure to talcum powder products can cause epithelial ovarian cancer.

III. METHODOLOGY FOR ASSESSING CAUSATION AND PRINCIPLES OF CAUSAL INFERENCE:

For this report, I followed the same methodology that I use in my clinical practice and research, a method that is generally accepted in the medical community. I used the same standards for evaluating and interpreting medical and scientific evidence, and I followed generally accepted standards in science and medicine for assessing causation, including consideration of the Bradford Hill viewpoints.

My causal assessment in this case is based on my background, training, education and experience as a physician and pathologist in interpreting, comparing, and weighing the totality of the available biologic, pathologic and epidemiologic evidence. I considered this evidence in the context of the Bradford Hill causation assessment viewpoints to reach an opinion regarding whether talcum powder products¹ can cause epithelial ovarian cancer.

Bradford Hill's discussion of a causal relationship includes strength of association, consistency, coherence, specificity, temporality, biological plausibility, dose-response, experimental evidence, and analogy as different "viewpoints" of a causal relationship between

¹ In my report, the term "talc" is used to refer to talcum powder products.

an exposure and a disease. Consideration of Bradford Hill's approach to causation, which I discuss in more detail below, supports general causation of talcum powder product exposure and ovarian cancer. The Bradford Hill causation viewpoints are not a checklist of requirements, and it does not call for a mechanical application of his 9 considerations for assessing a causal relationship; rather, it is properly understood as providing a framework for an assessment of the totality of the evidence leading to a judgment about causation. As Bradford Hill himself put it, "What I do not believe...is that we can usefully lay down some hard-and-fast rule of evidence that must be obeyed....None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as the *sine qua non*." I agree with that statement.

My methodology began with a systematic review of the medical literature to ascertain the relevant body of scientific evidence that I would consider. This included consideration of a large number of peer-reviewed publications reporting the results of human epidemiological studies investigating the association between talc exposure and ovarian cancer. I also considered and weighed other lines of evidence pertaining to explaining relevant, plausible, and likely mechanisms for how talcum powder product exposure causes ovarian cancer. This included carcinogenicity studies and data regarding talc and its constituents. Counsel for plaintiffs also provided me with medical literature to review, most of which overlapped with materials that I found independently through my own medical literature searches.

Relevance is not simply a yes/no proposition; it is a variable that ranges from not relevant to directly relevant, and there is a range between these extremes. Only a careful review of the evidence leads to an assessment of the degree of relevance. Much of science involves extrapolation and generalization from one study to the general population. The assessment of relevance is based on the extent that the study results are pertinent to the issue under consideration.

Human data is generally more relevant than animal data when assessing causation in humans. However, animal studies on exposure and disease are performed to advance our understanding of the human response to the same dose-adjusted exposure, and thus animal data is often relevant and important in that it can provide important information that forms part of the total evidence assessment. For example, if an exposure to talc in a rat causes inflammation, that could be relevant to assessing the effect in humans.

All observational studies have limitations, requiring careful interpretation. Reliability determinations focus on the degree of confidence in a study's internal validity. Reliability, like relevance, is not a yes/no proposition. For human epidemiologic observational studies, reliability assessments entail consideration of alternative explanations, including the role of chance and the likelihood that the results are affected by bias or confounding. Factors to be considered include: (1) Do we have reliable and appropriate measures of exposure; (2) do we have reliable assessments of disease; (3) do we have comparable groups for comparison; (4) have the investigators adjusted for potential confounding; (5) are the study results likely the result of a systematic bias; and, (6) does the study have enough exposures and sufficient power to detect an association if it exists?

I also consider the type of study design and whether it is suited to the question being researched. There is a general hierarchy of evidence, which I also consider, but study type and its position in the hierarchy will only have value if the study is otherwise relevant and reliable. For example, a randomized clinical trial may be the “gold standard,” but one must still look at whether the study does in fact provide a relevant and reliable result for the issue of interest (here, whether talcum powder products are capable of causing ovarian cancer).

In weighing the evidence other important considerations include: How does the study define, ascertain, and measure talc exposure? What type of study was it? Other considerations include: Has the study been or can it be replicated? Is the study result consistent with other studies? Has the study been published and has it been peer reviewed? Has the study been conducted on a relevant population? How does the study adjust for potential confounders and how does the study minimize or account for bias? Is there a potential for misclassification of exposure or disease based on the circumstances under which the data was gathered or analyzed? What is the potential that study results could be due to chance, bias, or confounding? Is there a statistical analysis, with a reported error rate? Were the results statistically significant, and, if not, are the results still important when considered with all other evidence from the perspective of overall consistency? What is the size of the study population? Is the study large enough to detect an association if it exists? Do the results make biologic sense? This is a list of examples of considerations for weighing the evidence, and is not intended to be comprehensive.

In weighing the evidence, I also consider the reported “P values” and confidence intervals (the result of statistical calculations), along with the reported relative risks and odds ratios, and other details about each study as explained above and below. The concept of “statistical significance” is often misunderstood. In assessing any statistical evidence pertaining to medical issues, medical and scientific researchers note whether certain findings are “statistically significant.” However, findings that are not “statistically significant” are often statistically and clinically important and should be considered and weighed along with other available evidence in making causal assessments. The concept of statistical significance using arbitrary cutoffs has no relationship to the strength or direction of an estimated association, and may have very little relationship with the actual validity of a study’s results. A “P value” of 0.05 or less is often considered statistically significant, whereas 0.06 is not.² I agree with the epidemiologists who consider this “cut-off” to be arbitrary, because, for example, the .01 difference between $p = 0.05$ and $p = 0.06$ is essentially the difference between a 5% vs. 6% probability that the observed association is due to the role of chance. Even where a confidence interval includes “1,” depending on the values of the lower and upper bounds of the confidence interval, the most likely interpretation of the study results may be that there is an association between an exposure and the increased risk of a disease.

² In epidemiologic studies, epidemiologists or statisticians calculate a P-value and/or 95% confidence interval (“CI”) for each risk estimate. Essentially, the P-value and the CI assess the likelihood that the observed association is due to the play of chance. A 95% CI means that if the same experiment is repeated many times, 95% of the time, the true value of the risk estimate will fall between the upper and lower bound of the CI. The narrower the CI, the more precise and reliable the risk estimate is considered to be.

Bradford Hill stated that “[n]o formal tests of significance can answer those questions [of causation]. Such tests can, and should, remind us of the effects of the play of chance... Beyond that, they contribute nothing...” Therefore, in weighing the evidence, I note the P-value and/or the confidence interval reported with a study’s results, and consider this to be an important piece of information for interpreting study results. I do not think it is appropriate to disregard results just because they do not meet an arbitrary statistical threshold, a view also held by the American Statistical Association (Wasserstein 2016).

All observational studies have limitations, and the potential for “bias” and confounding. The presence of some bias is not generally a basis for scientists to disregard a study. Instead, when interpreting a study, biases must be considered and assessed for the likelihood that they may obscure, diminish, or magnify a study result, so the direction and magnitude of any bias must also be considered where possible. Some biases will have the effect of obscuring or understating an association between exposure and disease. Typically, study investigators will include as part of their published paper reporting the study results, the important strengths and limitations (including their assessment of the role of bias, chance and confounding) in the study.

In weighing the evidence, I also consider the likelihood that the study may understate or fail to detect an association that did exist (a Type II error, often due to lack of “power”); or the converse, that a study result may overstate an association or find an association that is not real (Type I error). In interpreting studies that do not report an association with an increased risk of ovarian cancer, one issue is whether the results provide reliable evidence of the absence of an association. The only way for data to provide statistical reassurance about the absence of an association is, in the absence of any important systematic error in the data, for the upper bound of a reasonable confidence interval (such as a 95% confidence interval) to be close to the null value.

When a study finds an association between exposure and disease, causation is one explanation, but it is not the only explanation. Other explanations must be considered and assessed. When an observational study results in a reported association between exposure and disease (i.e., relative risk or odds ratio greater than 1.0), and if alternative explanations (*i.e.*, the role of bias, confounding and chance) are considered and determined to be unlikely explanations, then causation remains a likely explanation, subject to consideration of the Hill viewpoints. In order to reach an opinion that an association is causal between talc exposure and ovarian cancer, I considered whether there are other potential explanations that better explain the relationship and which are consistent with the totality of the scientific evidence. This assessment is informed by considering how a specific study fits into the overall totality of the evidence.

My opinions on causation are informed by a review of the strengths and limitations of the epidemiology evidence along with a review of other lines of evidence, including animal data and evidence on biological plausibility, likely mechanism(s) and dose/response. Thus, as part of my methodology, I have considered whether there is an alternative explanation to causation, based on an assessment of the totality of evidence. For example, I have considered whether the findings of the human epidemiologic studies are best explained by chance,

confounding or bias, when viewed separately, and most importantly, when viewed as a whole, and in light of the several lines of experimental evidence discussed in this report.

Based on my review of the totality of evidence, which I have weighed based on the considerations described above, I conclude with a high degree of medical and scientific certainty that exposure to talcum powder products can cause ovarian cancer. Causation is the best explanation for assimilating, assessing and weighing the totality of evidence. In reaching this opinion, I found it compelling that the epidemiologic studies that captured talc exposure consistently found an association between exposure to talc applied in the perineal area and epithelial ovarian cancer. The studies also provide persuasive evidence of a dose response effect, one of the viewpoints of causality discussed by Bradford Hill. There also is persuasive evidence of plausible and likely causal mechanisms for how talc exposure leads to ovarian cancer.

The other explanations for an association (other than causation) are bias, chance and confounding, and “reverse causation.”³ While it may not possible when looking at a single study to determine whether a recall bias, or a selection bias, or a potential confounder is materially affecting the results, I find it helpful to consider how each study fits into the whole. Here, multiple studies have been conducted in different populations, by different investigators, using different methods, and using different study types, and yet there is general consistency in the results. The vast majority of studies and meta-analyses find an association with an increased risk of ovarian cancer. Under these circumstances, viewing the evidence as a whole, the likelihood that the consistent finding of an association can be explained by bias, or chance or confounding is highly unlikely, especially in light of the results of the other lines of evidence.

Finally, as part of my methodology of considering alternative explanations for the evidence, I made an effort to understand the opinions of both the plaintiff and defense experts as concerning the issue of talc and causation of ovarian cancer. In that regard I have reviewed some plaintiff and defense expert testimony and reports, which are identified on my reference list. I also cited to the extensive medical literature I considered in connection with my work on this report.

IV. MECHANISM OF TALC’S CARCINOGENICITY

There is a plausible and likely biologic mechanism whereby talc causes inflammation which can lead to epithelial ovarian cancer. Chronic inflammation has been causally linked to a number of cancers. The evidence of the relationship between inflammation and cancer is based on many studies, including studies supporting the

³ In epidemiology, reverse causation is when the exposure-disease process is reversed; In other words, the exposure causes the risk factor. Here, the question is whether exposure to talcum powder products causes ovarian cancer or whether ovarian cancer causes increased usage of talcum powder products? I am not aware of any evidence to support a conclusion that reverse causation is a plausible explanation for the association between exposure to talcum powder products and ovarian cancer. The principal presenting symptom is abdominal bloating, which does not appear to lead to more talc use.

conclusion that inflammation plays a role in increasing the risk of epithelial ovarian carcinoma. As stated by the National Cancer Institute, “Over time, chronic inflammation can cause DNA damage and lead to cancer. For example, people with chronic inflammatory bowel diseases...have an increased risk of colon cancer.” The time interval between inflammatory response and presentation of cancer can be many years. Animal studies, particularly, may show granulomatous or other inflammatory reactions while not necessarily demonstrating neoplastic changes due to the time interval required for cancer to develop.

Studies have shown that pelvic inflammatory disease and endometriosis (known to cause an inflammatory reaction) increase the risk of ovarian cancer (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Lin 2011, Zhou 2017). Genofre et al. (2007) showed that talc can induce inflammation. Ness (1999) reported that inflammation of ovarian epithelium is a risk factor for ovarian cancer.

Inflammation has been implicated in carcinogenesis in several ways. Inflammation increases cytokines (Ness 1999). Shukla (2009) showed that nonfibrous talc can induce an inflammatory response that alters expression of genes in cancer pathways such as COX-2, ATF3, IL-6, and IL-8 in mesothelial cells. Further, inflammation increases oxidative stress (Ness 1999); Buz’Zard (2007) revealed that talc can induce oxidative stress and create reactive oxygen species (ROS), which in turn can induce ovarian neoplastic transformation in human ovarian cells. See also Saed (2017).

V. INFLAMMATION

Inflammation can produce toxic oxidants such as ROS that can be a source of mutagenesis to DNA. This damage to DNA by ROS is now accepted as a major cause of cancer, and has been demonstrated in ovarian cancer (Senthil 2004, Saed 2010, Saed 2017) as well as in breast and hepatocellular carcinoma (Waris 2006, Saed 2017). Talc exposure has been shown to cause a statistically significant increase in ROS in ovarian polymorphonuclear neutrophils (PMNs), resulting in a decrease in cell viability and neoplastic transformation of ovarian cells. The authors concluded that “talc increased proliferation, induced neoplastic transformation and increased ROS generation time-dependently in the ovarian cells.” (Buz’Zard 2007)

Thus, it is accepted that inflammation causes oxidative stress. Oxidative stress leads to the formation of ROS and reactive nitrogen species (RNS). Oxidative stress is an important factor in the initiation and development of several cancers, including ovarian cancer (Senthil 2004, Saed 2010, Saed 2018). The production of oxidants and free radicals affects cellular mechanisms that control cell proliferation and apoptosis, which in turn play a role in the initiation and development of several cancers (Saed 2018). ROS and RNS can induce genetic mutations and DNA damage, thus causing oncogenic phenotypes. Additionally, oxidative stress affects transcription factors that modulate the expression of genes important to the development and metastasis of cancer cells (Saed 2018). Oxidative stress is also known to activate certain signaling pathways, which are critical for the initiation and maintenance of the oncogenic phenotype (Waris 2006). In fact, the major source of cellular ROS, the NAD(P)H

oxidase family of enzymes, has been linked to the survival and growth of tumor cells in pancreatic and lung cancers (Reuter 2010, Rojas 2016). Pro-oxidant enzymes such as myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), and NAD(P)H oxidase have been associated with initiation, progression, survival, and increased risk in cancers such as breast, ovarian, lung, prostate, bladder, colorectal, and melanoma (Lengyel 2010, Fletcher 2017, Saed 2017, Saed 2018). Angiogenesis is critical for the survival of solid tumors and is also regulated by ROS (Reuter 2010, Saed 2017). Thus, it is clear that alteration of oxidative balance can provide an environment for cancer cell survival (Saed 2018).

Gene point mutations resulting in single nucleotide polymorphisms (SNPs), or a variation in a single base pair in DNA, have been associated with oxidative DNA repair genes and redox genes with cancer susceptibility (Klaunig 2010). There is evidence that genetic polymorphisms in genes with anti-tumor activity are associated with cell cycle genes and play a role in ovarian cancer etiology (Goode 2009, Notaridou 2011). There are associations of specific SNPs in oxidant and anti-oxidant enzymes with increased risk and survival of ovarian cancer (Belotte 2015, Fletcher 2017).

Higher levels of oxidants have been described in epithelial ovarian cancer (Malone 2006, Saed 2010, Jiang 2011). Fletcher et al. published an abstract in the March 2018 Reproductive Sciences that showed talc can generate a pro-oxidant state in both normal ovarian epithelial and ovarian cancer cells. In this study, there was a marked increase in mRNA levels of the pro-oxidant enzymes iNOS and MPO in talc treated ovarian cancer cell lines and normal ovarian epithelial cells, as compared to controls within 24 hours. There was also a marked decrease in the mRNA levels of the anti-oxidant enzymes catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase 3 (SOD3), but a marked increase in glutathione reductase (GSR) and no change in glutathione S-transferase (GST) in the talc treated ovarian cancer cell line and in normal ovarian epithelial cells compared to controls within 24 hours (Fletcher 2018). In addition to tumorigenic cells generating high levels of ROS that activate signaling pathways which promote proliferation, it is known that tumorigenic cells maintain a high level of antioxidant activity to prevent buildup of ROS to levels that could induce tumor cell death (Schieber 2014, Saed 2017).

ROS and RNS are normally neutralized by enzymes such as SOD, CAT, GST, glutathione (GSH), thioredoxin coupled with thioredoxin reductase, glutaredoxin, glutathione peroxidase (GPX), and GSR (Lei 2016). Glutathione S-transferase is involved in detoxification of carcinogens by catalyzing their conjugation to GSH (Lei 2016). The GS-X-MRP1 efflux pump, which removes toxins from cells, is known to be stimulated by the GSH/GSSG complex and this process has been investigated as a mechanism for the development of tumor chemoresistance (Ishikawa 1993, Circu 2012).

Further, data demonstrates that talc exposure caused a statistically significant increase in ROS in ovarian polymorphonuclear neutrophils (PMNs), which resulted in a decrease in cell viability and neoplastic transformation of ovarian cells (Buz'Zard 2007).

Additionally, inflammation induces increased cellular proliferation, giving rise to potential DNA replication errors. This is one of the ways increased lifetime ovulations increase the risk of epithelial ovarian carcinomas. Studies have shown that ovulation results in an inflammatory response to disruption of the ovarian epithelium with the release of inflammatory mediators that initiate cellular transformation and growth (Richards 2002). Endometriosis causes an inflammatory reaction (including macrophage activation, cytokine release, and expression of growth factors) and is a risk factor for clear cell (Figure 4) and endometrioid (Figure 5) ovarian carcinomas (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Edwards 2015). Studies have also shown that pelvic inflammatory disease (PID) is an ovarian cancer risk factor (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Lin 2011, Zhou 2017). Several prospective studies suggest that elevated serum levels of inflammatory markers such as CRP, TNF- α and IL-6 are predictive of development of ovarian cancer (McSorley 2007, Lundin 2009, Clendenen 2011, Toriola 2011, Poole 2013, Trabert 2014, Gupta 2016).

There also are some studies showing a protective effect of anti-inflammatory drugs on the risk of developing carcinoma, although some studies have failed to show a protective effect (Wu 2009). An analysis of many randomized controlled studies did show a reduced risk of developing carcinoma with aspirin use (Rothwell 2012). A 2014 article specifically evaluating ovarian carcinoma analyzed pooled data from 12 population-based case-control studies and showed a reduction of ovarian cancer risk with frequent aspirin and high-dose non-steroidal anti-inflammatory (NSAID) use (Trabert 2014). This further supports the role of inflammation in carcinogenesis, as this effect cannot be explained by other etiologies (Baandrup 2013, Trabert 2014).

Talc is not an inert substance. It has been shown to cause inflammation. Studies have shown increases in markers of inflammation following talc exposure (Allaire 1989, Genofre 2007, Arellano-Orden 2013). Talc is used therapeutically for patients with recurrent pneumothorax and pleural effusions based upon its ability to induce inflammation and adhesions. Injecting talc into the pleural space causes an inflammatory and granulomatous reaction, causing fibrosis and scarring which prevents further pneumothorax development (Antonangelo 2006, Najmunnisa 2007). This is mediated through the release of cytokines and chemokines (Nasreen 1998, van den Heuvel 1998), and the production of basic fibroblast growth factor (bFGF) (Antony 2004). It is worth noting that asbestos fibers are also known to initiate an inflammatory and scarring process within the pleura and peritoneum, which can eventually lead to neoplastic transformation of the mesothelium. The time interval between the initial inflammatory response for asbestos and talc and the development of cancer can be many years. Remote exposure will not necessarily mean there will be evidence of current inflammation or foreign body reaction when tissues are examined.

There also is evidence that talc induces macrophage TNF- α expression (Cheng 2000). Macrophages that express TNF- α promote ovarian tumorigenesis (Hagemann 2006). TNF- α is involved in chronic inflammation and induces mutations in vitro (Yan 2006). TNF- α induced chromosomal mutations occur mostly in cells with p53 aberrations (Yan 2006). Of note, high grade serous carcinomas typically have inactivating mutations in p53. Both talc and TNF- α induce macrophage expression of IL-8 (Nasreen 1998, van den Heuvel 1998), which attracts

neutrophils that then release ROS. This in turn causes a feedback loop between ROS generation and increased TNF- α expression, causing increased DNA damage (Xie 2000). This is an important line of biological experimental evidence supporting my causation opinion. The strongest association of talc and ovarian cancer is with invasive serous carcinomas, which commonly have p53 mutations, and TNF- α induced chromosomal mutations occur mostly in cells with p53 aberrations. Talc has been shown to induce macrophage TNF- α expression, which has been shown to promote ovarian tumorigenesis.

VI. ROLE OF IMMUNE SYSTEM IN CARCINOGENESIS

Studies have evaluated the protective role of the immune system in carcinogenesis, and in particular anti-MUC1 antibodies (Cramer 2005). MUC1 is a high molecular weight transmembrane protein expressed in many normal organs in a highly-glycosylated form. In cancer, including ovarian carcinoma, MUC1 is expressed at high levels in a poorly-glycosylated form. Anti-MUC1 antibodies are produced when high levels of the poorly-glycosylated form of MUC1 present to the immune system. Anti-MUC1 antibodies have been found in some cancers (Ho 1993, Dong 1997, Feng 2002) and have been associated with improved prognoses (Kotera 1994). Chronic processes including endometriosis, ovulation and talc exposure affect expression of MUC1 (Cramer 2005, Vlad 2006, Terry 2007). Decreased anti-MUC1 antibody production caused by these processes plausibly leads to immune-tolerance of an early ovarian carcinoma. Cramer et al. published a paper in 2005 that showed factors which increase the levels of anti-MUC1 antibodies lower the risk of ovarian carcinoma (Cramer 2005). Factors that decrease anti-MUC1 antibodies, such as incessant ovulation, have been associated with an increased risk of ovarian carcinoma (Terry 2007). Prospective data from the Nurses' Health Study (NHS) showed that tubal ligation increases anti-MUC1 antibodies, potentially by the procedure triggering the production of anti-MUC1, thus indicating another way tubal ligation exerts its protective effect. The study also showed that increased numbers of ovulatory cycles decrease anti-MUC1 antibodies, providing an explanation for the increased risk of ovarian cancer with increased lifetime ovulations (Pinheiro 2010). These studies provide evidence that MUC1 antibodies serve a role in the mechanism of and immune response in ovarian carcinogenesis. Because talc use is associated with a decrease in MUC1 antibody expression, the above is relevant to assessing the risk of talc use and ovarian cancer and provides further evidence supporting causation.

VII. COSMETIC TALC

Cosmetic talc has been used for decades, applied directly or indirectly to the genital region because of its high absorbency and softness (Langseth 2008).

Talc is a magnesium silicate hydroxide, characterized by water molecules in between silicate sheets. Asbestos is also a silicate mineral, but is somewhat morphologically distinct from talc and belongs to different silicate mineral groups. However, the chemical similarity of asbestos and talc led some researchers to postulate that both talc and asbestos could be causes of ovarian cancer (Graham 1967, Henderson 1971, Longo 1979). Early research into the possible link between talc and ovarian cancer was also instigated due to the fact that high

grade serous carcinoma, a type of invasive serous epithelial ovarian cancer (Figure 1), shown to be most commonly associated with perineal talc use, has striking morphologic similarities to mesothelioma (Figure 2), the tumor most associated with asbestos (Graham 1967). High grade ovarian serous carcinoma and mesothelioma express similar immunohistochemical markers, most notably cytokeratin pattern, WT-1 and calretinin. In fact, a great deal of surgical pathology literature deals with the nuances in differentiating peritoneal mesothelioma from high grade serous carcinoma. In the last few years, additional immunohistochemical panels have been developed that help distinguish between these two tumors (Laury 2010, Ordonez 2013), including PAX8, which is also expressed in fallopian tube epithelium. The morphologic and immunohistochemical similarities between asbestos and talc malignancies constitute another line of evidence supporting my opinion that talc exposure in the genital area causes ovarian cancer. Later in this report, I address the evidence that asbestos exposure can cause ovarian cancer.

VIII. TALC MIGRATION, TRANSLOCATION, INHALATION, AND LYMPHATIC TRANSPORT

In order for cosmetic talc applied to the perineum to reach the ovary or fallopian tube and exert a neoplastic effect, it needs to travel up through the vagina and uterus. It is known that substances can travel proximally through the female genital tract to the fallopian tubes and ovaries (Egli 1961, Venter 1979). Several studies have demonstrated the presence of talc in ovarian tissue (Henderson 1971, Henderson 1979, Mostafa 1985, Heller 1996) and even in the pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc (Cramer 2007). This is evidence that talc can be transported through the lymphatic system. Thus, another biologically plausible pathway is inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011).

There is evidence that serous ovarian cancers are actually of fallopian tube origin (Piek 2003, Kindelberger 2007, Kurman 2010, Erickson 2013). When considering whether talcum powder can cause ovarian cancer, this consideration is not critical. Talcum powder particulates reach both the fallopian tubes and ovarian surfaces by migrating proximally.

IX. TALC IN TISSUE

As mentioned above, several studies have demonstrated the presence of talc in ovarian tissue (Henderson 1971, Henderson 1979, Mostafa 1985, Heller 1996) and one study found talc in the pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc (Cramer 2007). In Cramer et al.'s 2007 paper, the methods used by Dr. John Godleski to identify talc particles in tissue are outlined (Cramer 2007).

Tissue was first analyzed using polarized light microscopy to identify birefringent particles within the tissue plane. Polarized light microscopy is used in routine practice in anatomic pathology. One of the most common uses in surgical pathology is for the identification of calcium oxalate calcifications in breast tissue. In some lesions of the breast,

ranging from benign to malignant, calcifications occur that can be a marker for disease and are discovered on breast mammography. After mammography reveals calcifications and the radiologist determines them to be suspicious for disease, the area with calcifications is biopsied. The biopsy sample is then X-rayed to confirm the presence of the calcifications, and then submitted to the pathology laboratory for histologic analysis and diagnosis. The pathologist correlates the calcifications seen under the microscope with those in the specimen X-ray to be sure the calcifications the radiologist identified are visualized in the tissue sample. Calcium oxalate is a certain type of calcification that is not easily seen on light microscopy. If there appears to be a discrepancy between the tissue under light microscopy and the specimen X-ray (lack of calcifications under light microscopy), the pathologist will use polarized light microscopy to help identify calcium oxalate crystals, which are birefringent. Similarly, Dr. Godleski used polarized light microscopy to identify birefringent material that could be further analyzed using SEM and EDX.

SEM was more commonly used in surgical pathology before immunohistochemical studies were routinely used and before the common availability of molecular testing. However, SEM is still routinely used as an important diagnostic tool in areas of pathology in which immunohistochemical studies and molecular testing are less helpful, such as medical renal pathology, neuromuscular disorders and rare tumors. SEM uses electrons for imaging, analogous to light microscopy using light. SEM allows for much greater magnification (>100,000X) than light microscopy.

EDX is a qualitative and quantitative chemical analysis used in conjunction with SEM. It detects X-rays emitted from the sample during electron scanning to determine the elemental composition of the particle being examined. EDX is widely used in many biomedical areas, as it provides precise information on the chemical composition of subcellular structures that can be correlated with their SEM images (Wyroba 2015).

In Cramer et al 2007, the authors analyzed four pelvic lymph nodes from a 68 year old woman with ovarian papillary serous carcinoma and a small component of clear cell carcinoma. She had been a daily talc user for 30 years, having applied it to underwear and sanitary napkins. The lymph nodes showed birefringent particles via polarized light microscopy and were then analyzed by SEM and EDX. This showed magnesium and silicate signatures consistent with talc (Cramer 2007). Of note, there are similar studies performed with asbestos fibers in tissue sections (Roggli 1983, 1986).

Additionally, studies have shown Raman microscopy can be used to identify talc spectra in routinely processed, but unstained, histologic pathology specimens. Raman microscopy uses laser light to elicit the chemical and microstructural characterization of materials (Campion 2018).

Although the presence of talc particles found in ovarian cancer tissue does not prove that the talc played a causal role, when considered with the other lines of evidence supporting causation discussed in this report, the presence of talc in ovarian cancer tissue is certainly consistent with causation and provides additional evidence in support of a causal relationship between talcum powder products and ovarian cancer.

X. EPIDEMIOLOGICAL DATA REGARDING TALC USE AND OVARIAN CANCER:

As detailed below, there is consistent evidence from multiple observational studies, pooled analyses, and meta-analyses that exposure to talcum powder products is associated with an increased risk of ovarian cancer. When combined and considered with the biological evidence described above, this consistent epidemiologic data from multiple studies provides strong evidence that the association is, in fact causal.

Although occasional studies have not found talc powder applied to the perineum or contraceptive diaphragms⁴ to be a significant risk for developing ovarian cancer, as detailed below, most have found an association, and the cumulative evidence from these studies, when considered with the other lines of evidence discussed above, provides strong and compelling evidence of a causal association.

XI. CASE-CONTROL STUDIES

Henderson first observed talc particles embedded in both ovarian tumors and normal ovaries (Henderson 1971). The first epidemiologic study on genital talc use and the risk of ovarian cancer was a case-control study by Cramer et al. (Cramer 1982). In this study, 215 women with epithelial ovarian cancer and 215 age-matched controls were questioned about talc use on the perineum and/or on sanitary napkins; 42.8% of ovarian cancer patients reported regular use of talc (prior to developing ovarian cancer) compared to 28.4% of controls, with an odds ratio (OR) of 1.92 (95% confidence level (CI) 1.27-2.89). The greatest risk in this study occurred in women who had used talc powder both directly on their perineum and on sanitary napkins compared to women who had no history of talc powder use; the odds ratio was 3.28 (CI 1.68-6.42). Of note, Cramer et al. did not exclude women from the control group who had a history of hysterectomy or other “pelvic surgeries” if the patient had intact ovaries by self-report. This could potentially lead to an underestimate of the risk of talc and ovarian cancer, as the controls may have had other confounding factors. They did control for confounding factors such as age, parity, religion, education, age of menarche, oral contraceptive use, hormone replacement therapy and smoking history.

While case control studies may have limitations with selection bias, Cramer et al. state “Our sample of cases represents more than 50% of ovarian cancer cases diagnosed

⁴ It is likely that studies based on talc with diaphragm use are generally limited to use by women for birth control purposes. This will not capture use before or after the women’s use of diaphragms for contraceptive purposes, a potential of multiple years that will not be captured in the study. Even for the years when women are using diaphragms, it is likely they are not using diaphragms for birth control on a daily basis. Therefore, diaphragm studies are likely to be biased toward the null; i.e., likely to understate talc exposure, and for that reason are likely to fail to detect an association that actually exists or understate the magnitude of risk.

in Boston residents in the study period. Therefore, it is difficult to conceive of a plausible bias in the selection of cases that would yield this excess use of talc.” (Cramer 1982)

In additional to the Cramer 1982 study, numerous other case-control studies addressing talc use and ovarian cancer have shown statistically significant odds ratios greater than 1, indicating talc use is associated with an increased ovarian cancer risk (Harlow 1989, Booth 1989, Harlow 1992, Chang 1997, Cook 1997, Green 1997, Godard 1998, Cramer 1999, Gertig 2000, Ness 2000, Mills 2004, Merritt 2008, Wu 2009, Moorman 2009, Rosenblatt 2011, Kurta 2012, Houghton 2014, Wu 2015, Schildkraut 2016, Cramer 2016).

In a 1983 letter to the editor in JAMA in response to the 1982 Cramer study, Hartge and Hoover state that they found an association between genital talc use and ovarian cancer with a RR of 2.5, but the sample size was small (7 cases to 3 controls), resulting in a wide confidence interval (0.7-10.0). They did not find an association between ovarian cancer and body talc use or talc use on diaphragms, but again the sample sizes were small (Hartge 1983). Similarly, a study published by Tzonou et al. in 1983 showed no association between perineal talc use and ovarian cancer (RR 1.05; CI 0.28 to 3.98) but the frequency of reporting talc use was low in the study population, thus the wide CI (Tzonou 1983).

Whittemore et al. published a case-control study in 1988 that showed a RR of perineal talc use and ovarian cancer of 1.40, with a p value of 0.06. They did not see an increased risk of ovarian cancer in women who used talc on sanitary napkins or diaphragms. They did see an increased risk of ovarian cancer in women who used perineal talc for 1 to 9 years compared to those who used it for a shorter period (RR 1.60, p=0.05, CI 1.00-2.7) but did not see an increase with perineal talc users greater than 10 years (RR 1.11, p=0.61, CI 0.74-1.65). A strength of this study is that participants were not only asked about their history of talc use, but also about their history of cigarette smoking, coffee and alcohol consumption, thus addressing recall bias. A possible limitation of this study is the fact that the control group was a combined group of two separate control groups: one hospital based from the hospitals where the cases were admitted, and one community based. It was not described for what conditions the hospital controls were admitted (Whittemore 1988).

In 1989 Booth et al. published a study that showed an increased risk of ovarian cancer in daily talc users (RR 1.3, CI 0.8-1.9) and weekly talc users (RR 2.0, CI 1.3-3.4) as opposed to monthly (RR 0.7, CI 0.3-1.8) and rare (RR 0.9, CI 0.3-2.4) users. There were limitations of this study, however; participants were limited to women younger than 65 who had been diagnosed within the two years prior to interview. The data was adjusted for age in 5 year stratas and socio-economic status, but socio-economic status was based upon husband’s career if married and participant’s career if never married. Strengths, however, included queries of hormone replacement therapy, type of contraceptive use, and duration of oral contraceptive use; this helps to address recall bias. Additionally, hospital-based controls admitted for gynecologic disease and breast cancer,

among other diseases, were excluded and hospital admission diagnoses were listed (Booth 1989).

Harlow's 1992 study included 235 women with epithelial ovarian cancer and compared them to 239 control women matched for age, race and residence. After adjusting for age, parity, weight, education, marital status, religion, use of sanitary napkins and douching, it was found that talc use increased the ovarian cancer risk by 50% (OR=1.5, CI 1.0-2.1). Harlow's 1992 study also involved a dose-response effect; duration and frequency of perineal talc use was calculated into lifetime talc applications. Lifetime application ORs, when compared to control women with no perineal talc exposure, were 1.3 for <1000 (CI 0.7-2.7), 1.5 for 1000-10,000 (CI 0.9-2.4) and 1.8 for >10,000 (CI 1.0-3.0) (Harlow 1992). A dose response effect is a consideration in assessing causation. Harlow, Terry (2013) and Wu (2015) studies provide clear evidence of a dose effect. Particular strengths of the Harlow study are the number of potential confounding factors adjusted for and the detailed history on type of use and duration of use. Women with body exposure (non-genital) were considered non-exposed. Additionally, in the Harlow study, women were also asked about dietary and smoking histories, which helps to address potential recall bias.

Rosenblatt et al. published a study in 1992 that showed an increased risk of ovarian cancer with talc use (OR 1.7, but a small sample size with CI 0.7-3.9) (Rosenblatt 1992). In the Rosenblatt study, participants were also asked about oral contraceptive use and hormone replacement therapy, which helps to address potential recall bias. Another study published in 1992 by Chen et al. evaluated the association between talc use and ovarian cancer in a Beijing population. They found a RR of 3.9 in women with a history of use greater than 3 months, but the sample size was small with a 95% CI of 0.9-10.63. They also included dusting powder to the lower abdomen as well as perineum (Chen 1992), which would likely understate the magnitude of the association.

A 1997 study published in the journal *Cancer* by Chang et al. analyzed 450 patients with either ovarian borderline tumors or invasive ovarian carcinomas and showed an increased risk of tumor in women with either direct perineal application of talc or talc use on sanitary napkins (OR=1.42 after adjusting for age, parity, tubal ligation, hysterectomy, duration of oral contraceptive use, length of breastfeeding after pregnancy, and family history of ovarian cancer CI 1.08-1.86). For invasive ovarian carcinomas, the adjusted OR was 1.51 (CI 1.13-2.01). For borderline tumors, the adjusted OR was 1.24 (CI 0.76-2.02) (Chang 1997). The authors found that a borderline-significant association between duration of talc exposure and risk (OR 1.09, 95% CI 0.98-1.21, per 10 years of exposure). No significant association was found between frequency of exposure and risk. In comparing invasive and borderline carcinomas, risk remained elevated for both carcinoma types. The study did not assess for non-genital talc use. A particular strength of this study is that the same questions regarding talc use were asked about cornstarch use; they found no significant risk of ovarian cancer with cornstarch use (OR 0.31, CI 0.06-1.66), although only 1% of the populations reported using cornstarch (Chang 1997). Still, this helps to reconcile potential confounding risk factors of ovarian cancer in people more likely to use perineal powder. The interviews with participants also included taking

histories on oral contraceptive use and hormone replacement therapy, which helps to address recall bias.

Cook et al. also published a study in 1997 that evaluated 313 women with epithelial ovarian tumors (both invasive and borderline) and 422 controls. Only white women were included. They found that there was an increased risk of ovarian cancer with direct perineal powder dusting of 60% (OR=1.6, CI 1.1-2.3) and 90% (OR=1.9, CI 1.1-3.1) for genital deodorant sprays sprayed directly onto the perineum. Lifetime number of talc applications provided evidence of dose-response: a statistically significant increased risk (OR=1.7, CI 1.0-2.9 for less than or equal to 500 applications, OR=2.6, CI 0.9-7.6 for greater than 500 applications). A strength of this study is that participants were asked about smoking and contraceptive use, which helps to address recall bias. A limitation of this data is that all types of powder were included, such as cornstarch, "baby powder," "deodorant powder," and "scented body/bath powder." However, the authors state, "No specific type of powder used for perineal dusting, diaphragm storage, or on sanitary napkins was strongly related to ovarian cancer risk, although there was a suggestion of an elevated risk associated with any use of talcum powder and bath/body powders (RR = 1.6, 95 percent CI 0.9-2.8, and RR = 1.5, 95 percent CI 0.9-2.4, respectively)." (Cook 1997)

In 1997, an Australian study performed by The Survey of Women's Health Study Group enrolled 824 women with epithelial ovarian tumors, both invasive and borderline, and 855 controls. They found that the risk of ovarian cancer was highest among women who were talc users and had not undergone surgical sterilization (RR=1.3, CI 1.1-1.7) after adjusting for age, parity, duration of oral contraceptive use, BMI, smoking, education and family history of ovarian cancer. The risk was lowest in women who had not applied talc to their perineum and had either a tubal ligation or hysterectomy (RR=0.6, CI 0.50-0.84) (Green 1997). Because tubal ligation limits transport of talc fibers to the ovary, this study, with a finding of a protective effect in women with tubal ligation, provides an important piece of additional evidence. Strengths of this study include high response rate (90% of cases and 73% of eligible controls) and the verification of past surgical procedures by contacting participants' surgeons. Additionally, participants were asked questions about other potential exposures such as smoking histories and pelvic inflammatory disease, which helps to address recall bias. Limitations include a lack of data on quantity of talc use.

In 1999, Wong et al. published a paper that did not show a consistent association with talc powder and ovarian cancer, evaluated by length of use as follows: talc use for 1-9 years (OR 0.9; 95% CI 0.6, 1.5), 10-19 years (OR 1.4; 95% CI 0.9, 2.2), or more than 20 years (OR 0.9; 95% CI 0.6, 1.2). This was after adjustment for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy. However, this study would tend to understate the magnitude of an association with genital talc use because it included talc use on thighs as well as genitals. The study used hospital controls, which raises a question of whether the controls were comparable to the cases (Wong 1999).

As part of Cramer et al.'s 1999 study, 563 women with newly diagnosed epithelial ovarian cancer were compared to 523 controls, and showed that perineal talc users had a significantly increased odds ratio for epithelial ovarian cancer (OR=1.60, CI 1.18-2.15). The effect of talc use was even stronger for invasive serous carcinoma (OR=1.70, CI 1.22-2.39). This was after adjusting for age, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. The higher risk for women with invasive serous carcinoma was replicated in other studies, and this is an important finding in these studies because of its specificity. In addressing potential recall bias, Cramer et al. state, "...recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias... It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer.... Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or [oral contraceptive] use and little variability of the association by these and other variables." (Cramer 1999)

Ness et al.'s 2000 study evaluated 767 women with ovarian epithelial borderline tumors and ovarian invasive cancer compared to 1367 controls. Consistent talc use, defined as at least once per month for six or more months, increased the ovarian cancer risk by 50% (OR=1.5, CI 1.1-2.0) when applied to the perineal area directly and increased the risk by 60% (OR=1.6, CI 1.1-2.3) when used on sanitary napkins. This is after adjusting for age, parity, tubal ligation, hysterectomy, duration of oral contraceptive use, breast feeding and family history of ovarian cancer (Ness 2000). One explanation of the increased risk of talc use on sanitary napkins is that sanitary napkins may keep a larger amount of talc closer to the vagina over the course of several hours, thus increasing the risk of entry to perineum, while talc directly applied to the perineum may more easily disperse, however, many studies have failed to show an increased risk in ovarian cancer in participants whose only exposure to talc was on sanitary napkins. The strengths of this study include addressing multiple confounding factors. No dose-response was found; weaknesses include that only duration information was available, and genital/rectal talc use durations reported were combined with duration of use on the feet. Additionally, women who used just once per month were categorized as a user. These weaknesses may cause an underestimation of risk, and may have accounted for the lack of dose-response found.

Mills et al. published a study in 2004 that evaluated the association between talc use and ovarian cancer among 256 cases of ovarian cancer as compared to 1122 controls. Women diagnosed with invasive epithelial ovarian cancer with a history of genital talc use had an increased risk of 51% (OR=1.51, CI 1.07-2.12). This increased risk increased to 77% (OR=1.77, CI 1.12-2.81) for women diagnosed with invasive serous carcinoma.

Dose-response effects were also found. Increasing frequency of use was associated with increasing risk; women who reported use 4–7 times per week had a 74% elevation in epithelial ovarian cancer risk (p for trend = 0.015). However, the risk decreased between the second and third categories of use (from “rarely to several times per month” and “1–3 times per week” at 1.34 (CI 0.87–2.08) to 1.16 (CI 0.74–1.81), respectively). Duration of use of talc was also associated with increased risk, although the risk peaked among those reporting 4–12 years of use and declined somewhat among those reporting longer duration of use (p for trend = 0.045). Cumulative use also demonstrated an uneven association with risk of epithelial ovarian cancer in that the point estimates peaked in the second and third quartiles of intensity but declined in the highest quartile of use. These findings were after adjusting for age, race/ethnicity, duration of oral contraceptive use and duration of breast feeding. Yet, there wasn’t adjustment for first relative history of breast or ovarian cancer, pregnancy history, parity, BMI, hysterectomy, tubal ligation or hormone replacement therapy; according to the authors, the Hosmer-Lemshow goodness-of-fit tests revealed that after terms for duration of oral contraceptive use and duration of breast-feeding were added to the models, fit was not improved by the addition of these variables, nor were the estimated odds ratios altered by the addition of several of these variables (Mills 2004). However, the fact that participants were queried about other possible exposures such as hormone replacement therapy helps to address potential recall bias.

In Wu et al.’s 2009 study, women were found to be at increased risk of ovarian cancer if they had a history of prior perineal talc use, with the risk increasing significantly in those with long term (20+ years) and frequent (at least daily) use with a relative risk of 2.08 (CI 1.34–3.23), i.e., a dose effect. The authors did find an increased risk in women who used talc on sanitary napkins (RR 1.61, CI 0.93–2.78), underwear (RR 1.71, CI 0.99–2.97) and diaphragms/cervical caps (RR 1.14, CI 0.46–2.87). There was a stronger association between talc use and serous ovarian cancer; the relative risk with any talc use was 1.70 (CI 1.27–2.28). Strengths of this study include the adjustment for multiple possible confounding factors (age, race/ethnicity, education, age of menarche, parity, oral contraceptive use, family history of ovarian or breast cancer, menopausal status and tubal ligation). Another strength was that participants were queried about NSAID and endometriosis histories, helping to address potential recall bias. The authors mention in their discussion that the participation response was “modest,” possibly leading to selection bias (Wu 2009).

Rosenblatt et al. published a study in 2011 that showed an overall increased risk of ovarian cancer in women who used talc after bathing (OR=1.27, CI 0.97–1.66) with a more pronounced risk in women diagnosed with mucinous borderline tumors (OR=1.78, CI 0.98–3.23) and serous borderline tumors (OR=1.47, CI 0.85–2.55) (serous borderline tumor illustrated in Figure 3). They did not see an increased risk by extent of use, defined as years in which powder was used, or as lifetime number of applications. There was no alteration in the risk of ovarian cancer associated with other types of powder exposure such as sanitary napkins or diaphragms. This study did not find an increased risk of invasive serous carcinoma (OR 1.01, CI 0.69–1.47). (Rosenblatt 2011) A strength of this

study is that participants were queried about other potential exposures (smoking, alcohol and endometriosis histories), which helps to address recall bias.

In 2012, Kurta et al. evaluated talc use and the risk of ovarian cancer, although their main focus of the study was the associated risk of ovarian cancer with fertility drug use. They found a OR of 1.40 (CI 1.16-1.69). Since talc was not the primary focus of this study, duration of use was not considered; participants were categorized as talc users if they had ever used talc versus never-users. Perineal talc use was only generally defined as dusting powder or deodorizing spray on the genital or rectal areas, sanitary napkins, underwear, or diaphragms or cervical caps (Kurta 2012). A strength of this study is that its main focus was on fertility drug use; participants were asked about exposures such as fertility treatments and hormone replacement therapy, which helps to address potential recall bias.

Wu et al. published a paper in 2015 that evaluated talc use and invasive ovarian cancer in white, Hispanic and African American women. They found that talc use was more common in African-American women (44.1%) than in non-Hispanic whites (30.4%) or Hispanics (28.9%) ($p=0.001$). The results showed ORs of 1.41 for white women (CI 1.21-1.67), 1.77 for Hispanic women (CI 1.20-2.62) and 1.56 for African American women, although the CI for African American women was 0.80-3.04. Overall, the OR was 1.46 (CI 1.27-1.69). However, the response rate and sample size for this study was somewhat small, and participants with less than one year of use were categorized as never users (Wu 2015).

In 2016, Schildkraut et al. published a paper as part of the African American Cancer Epidemiology Study (AACES), a case-control study of epithelial ovarian cancer in African American women. According to the authors, due to the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), the authors merged this exposure category with those who reported use of both non-genital and genital powder, creating an exposure category of “any” genital powder use, but separately evaluated the categories as “only” or “any” genital powder use. They reported an increased risk of ovarian cancer in “any” genital powder users (OR=1.44, CI 1.11-1.86) and noted a statistically significant dose response effect for both duration of use and lifetime applications. A strength of this study was adjustment for multiple confounding factors such as age, education, BMI, parity, tubal ligation, OCP use, first degree relative with breast or ovarian cancer, and interview year (taking into account litigation cases in the year 2014). Participants were also asked about hormone replacement therapy, another potential exposure, thus helping to address potential recall bias. A weakness of this study is that participants were considered “regular users” if they reported using cornstarch, baby or deodorizing powders at least one time per month for at least 6 months, and “never users” if they did not, leading to possible misclassification that would bias toward the null (Schildkraut 2016).

The totality of the results of the case-control studies support a causal link between talc and ovarian cancer. When observational studies find an increased risk of disease with a certain exposure, the possible reasons are chance, bias, confounding and causation.

There is a general consistency of these individual studies; the ORs have been of similar magnitude in studies spanning different decades, in different populations, with different study designs, by different investigators, over different continents and with adjustment for multiple confounders. Therefore, the possibility that the association between perineal talc use and ovarian cancer is due to chance is extremely unlikely.

Although retrospective case-control studies potentially have an element of recall bias and other potential biases, again, the consistency of results across these studies and populations makes recall and other bias an unlikely explanation. During the period that the majority of studies were conducted, public awareness of the link between talc and ovarian cancer was limited. There is also a much stronger and statistically significant association of perineal talc use and ovarian cancer in studies that compared all-body talc use to perineal use. The finding in some studies that serous carcinoma has a stronger association with perineal talc exposure than other histologic subtypes of ovarian cancer also argues against recall bias, as participants are very unlikely to have knowledge about the histologic subtyping of ovarian cancer. In addition, in studies where participants are asked to recall multiple exposures, not just talc exposure, this will minimize the risk of recall bias because it is unlikely that participants will differentially recall talc exposure but not other exposures, especially if they are blinded to the study hypothesis. Studies using trained interviewers, structured interview questionnaires, and blinding of both study participants and the interviewers to the study hypotheses will also limit the potential for recall bias.

Selection bias (which can arise based on differential participation rates or other differences between comparison groups) accounting for the results across studies is also unlikely. To see such consistent associations between perineal talc use and ovarian cancer, there would need to be strong associations between participation and perineal talc use, and strong differences amongst cases and controls due to selection bias only - this would be extremely unlikely to produce such large biases across studies. Most studies adjusted for confounders, with the majority adjusting for age, BMI, and parity among others. With chance, bias, and confounding being unlikely explanations for the association of perineal talc use and ovarian cancer across multiple studies, this leaves causation as the most likely explanation.

XII. COHORT STUDIES

The talc literature includes several cohort studies reporting the relative risk for perineal talc use and risk of ovarian cancer, including the Nurses' Health Study, the Women's Health Initiative and the Sister Study (Gertig 2000, Gates 2008, Gates 2010 and Gonzalez 2016). There were several important limitations of these studies to adequately capture risk of ovarian cancer based on the methodology used by the researchers to assess talc exposure.

The Gertig study evaluated prospective cohort data from 78,630 women, and although there was a 12% overall increased risk of ovarian cancer in women with a history of daily genital talc use, this was not statistically significant. Yet, the investigators

reported a statistically significant increased risk of invasive serous carcinoma (RR=1.4, CI 1.02-1.91) after adjusting for age, parity, duration of oral contraceptive use, post-menopausal hormone use, tubal ligation, BMI and smoking (Gertig 2000). Additionally, the lack of statistical significance of overall ovarian cancer risk may be due to several important limitations with this study, including the fact that the question of talc use was only in one questionnaire in 1982 and did not include questions on duration of use. Thus, a person who used talc just a few times would be included with women who used talc daily over a long duration, and this will have the effect of understating the risk. In fact, in a follow-up 2008 report, Gates et al. noted that since talc exposure was only referred to once in questionnaires, it is possible that some participants were misclassified with respect to their talc use or that some women may have started talc use after 1982 and thus these women would not be included in the talc user group (Gates 2008). This would understate the risk and decrease the calculated statistical significance of talc-related ovarian cancer. An additional review of the Nurses' Health Study published by Gates et al. in 2010 studied 876 cases of ovarian cancer and talc use, although this was not the primary focus of the study. This study found an overall increased risk of ovarian cancer with talc use (RR=1.06), but found an increased risk for mucinous tumors (RR=1.50) (Gates 2010) (mucinous carcinoma illustrated in Figure 6). Again, the weaknesses in the study include the fact that talc use was only queried once in 1982, and the authors state themselves that the limited data on talc use may have influenced the observed association with ovarian cancer.

Cohort studies like the Nurses' Health Study, Women's Health Initiative Study and the Sister Study have some drawbacks when studying rarer diseases compared to case-control studies that have been described above. Cohort and case-control studies are both observational, and both have strengths and limitations. Cohort studies begin when all participants are free of the disease in question. After a follow-up period, those that have the disease being studied are compared by exposure risk being studied to those who did not develop the disease. Although this helps to ensure exposure predates disease, there may be a lack of data if the disease is rare or if there is a long latency period between exposure and disease presentation/diagnosis, as is the case of ovarian cancer and talc. In contrast, in case-control studies, patients already have the disease being studied and are compared to controls who do not have the disease with a focus on the rates of exposure to the agent of interest (here, talcum powder products) in the cases as compared to the controls. A possible limitation of case-control studies in the context of ovarian cancer and talc is the fact that exposure to talc is self-reported and subject to potential recall bias.

The case-control studies may unavoidably have recall bias, as talc use was self-reported by participants. In their 2018 meta-analysis discussed below, Penninkilampi et al. noted that in some studies, interviewers were not blinded to cases and controls and many studies did not describe whether their controls had a personal history of previous ovarian cancer. However, they also noted that in general, controls were well matched to cases by other possible confounding factors such as age, geographic, location and ethnicity (Penninkilampi 2018).

In the 2008 Gates paper, women with certain variants in glutathione S-transferase M1 (GSTM1) and/or glutathione S-transferase T1 (GSTT1) were shown to have a higher risk of talc-associated ovarian cancer. Glutathione S-transferases catalyze the conjugation of glutathione to numerous potentially genotoxic compounds. Individuals with homozygous deletions of GSTM or GSTT have reduced or no glutathione S-transferase activity and may be unable to eliminate electrophilic carcinogens as efficiently (Coughlin 2002). The 2008 Gates study included 1,175 cases and 1,202 controls from a case-control study and 210 cases and 600 controls from the prospective Nurses' Health Study. Participants were genotyped for the GSTM1 and GSTT1 gene deletions and three NAT2 polymorphisms. Regular talc use was associated with increased ovarian cancer risk in the combined study population (relative risk=1.36, CI 1.14-1.63; p-trend<0.001). In the pooled analysis, the association of talc and ovarian cancer was stronger among women with the GSTT1-null genotype (p-interaction=0.03), particularly in combination with the GSTM1-present genotype (p-interaction=0.03). There was no clear evidence of an interaction with GSTM1 alone or NAT2. Without talc exposure, these genes were not clearly associated with risk of ovarian cancer (Gates 2008). The specificity of the findings linking the genetic polymorphisms with ovarian cancer subtype most associated implicates yet another aspect of the Bradford Hill viewpoints.

As previously detailed, the Nurses' Health Study also showed that genital talc use was associated with lower levels of anti-MUC1 antibodies, which has been associated with an increased risk of ovarian cancer. As part of the Nurse's Health Study, Pinheiro et al. published a paper in 2010 that showed increasing anti-MUC1 antibody levels were associated with a nonsignificant trend for a lower risk of ovarian cancer with highly significant heterogeneity by age (p-heterogeneity=0.005). The authors concluded that anti-MUC1 antibodies evaluated several years prior to diagnosis may be associated with lower risk of subsequent ovarian cancer in women less than 64 years old at assessment (Pinheiro 2010). Cramer et al. 2005 study showed factors which increase the levels of anti-MUC1 antibodies lower the risk of ovarian carcinoma (Cramer 2005). These findings provide evidence that a plausible mechanism for talc-associated ovarian cancer is a down-regulated immune response to MUC1, and thus an immune tolerance of an emerging MUC1-expressing tumor.

The Women's Health Initiative Observational Study (WHI-OS) did not report a statistically significant increased risk of ovarian cancer with talc use (Houghton 2014). In that study, 61,576 women were enrolled and 429 developed ovarian cancer during follow-up. The study did find a 12% increased risk of ovarian cancer in perineal talc users (RR=1.12, CI 0.92-1.36), but it was not statistically significant. However, the risk of developing serous carcinoma was increased by 18% (RR=1.18, CI 0.89-1.56), and by 13% for invasive serous carcinoma (RR=1.13, CI 0.84-1.51). Additionally, 101 cases were categorized histologically as "other," including tumors that were self-reported, not validated and potentially may not have even been primary ovarian tumors. This would bias the risk estimate of talc use in ovarian cancer in this study toward the null by including cancers or other tumors potentially from other sites; in other words, non-specific cancer types may have been included that are not known to have an association with talc use. Another weakness of the study is that although the authors did evaluate the

effect of duration of use of genital talc on the risk of ovarian cancer, they did not evaluate frequency of use. Thus a woman who used talc for twenty years once a month would be treated the same as a woman who used it every day for twenty years. This will tend to understate or obscure the true risk of long term, frequent use. The study also was of an older age group (50-79) who were post-menopausal at time of enrollment, which adds selection bias.

Another study in which the effect of talc use on the risk of ovarian cancer is likely diluted or understated is the Sister Study, published by Gonzalez et al. in 2016. In this study, there was no reported association between perineal talc use and subsequent ovarian cancer. The study only enrolled women with a full or half-sister who had been diagnosed with breast cancer. BRCA1 and BRCA2 mutations are associated with a markedly increased risk of both breast and ovarian cancer, and in the Sister Study, women were not tested for this mutation. Most of the ovarian cancers associated with BRCA mutations are of the invasive serous subtype, the same subtype most strongly associated with talc use in prior studies. By not testing the women for the genetic mutation, the Sister Study analyzed a population of women with an increased risk of having a BRCA mutation (by having a first degree relative, or sister/half-sister, with breast cancer), a significant confounding factor that was not considered. Another limitation of this study is that the mean follow-up was 6.6 years, a very short period considering the generally long latency period of ovarian cancer. The Sister Study did find an increased risk in ovarian cancer in women who douched, providing evidence supporting the link between particulate route of access to the ovary/fallopian tube. The histologic subtype of the ovarian cancer was also not evaluated. Further, similar to the other cohort studies, the Gonzalez 2016 study failed to adequately capture both duration and frequency of talc exposure as participants were only asked if they used talc in the last 12 months.

XIII. META-ANALYSES REGARDING TALC USE AND OVARIAN CANCER:

Meta-analyses are an important tool that combines study results from multiple studies to develop a single result that has greater power to detect a more precise estimate of risk. Several meta-analyses have been published on the association between talc use and ovarian cancer, all showing an increased risk (Harlow and Cramer 1992, Gross and Berg 1995, Cramer and Harlow 1999, Huncharek 2003, Langseth 2008, Berge 2018, Penninkilampi 2018).

In 1992 Harlow and Cramer published combined results from six case-control studies of the association between talc use and ovarian cancer that were performed between 1982 and 1989. The association was statistically significant (OR=1.3, CI 1.1-1.6) (Harlow 1992). In 1995, Gross and Berg published a meta-analysis that included the six case-control studies evaluated in the 1992 Harlow and Cramer paper, plus three additional studies. This produced a statistically significant increased risk (OR=1.27, CI 1.09-1.48) (Gross 1995). Of note, this study was supported in part by Johnson and Johnson, raising the issue of funding bias.

Cramer published another meta-analysis in 1999 that included the nine studies in Gross and Berg's 1995 paper plus five additional ones performed through 1999. The overall risk of ovarian cancer in talc users was found to be increased at 36% (OR=1.36, CI 1.24-1.49) (Cramer 1999).

Huncharek et al. performed a meta-analysis in 2003 that added five new studies and included all of the previous studies except the 1983 Hartge and 1996 Shushan studies. The OR in this study was 1.33 (CI 1.16-1.45). Interestingly, the authors concluded that even with this statistically significant OR, the data "do not support the existence of a causal relationship" between talc use and ovarian cancer (Huncharek 2003). In a subsequent paper published by Huncharek et al., support from Johnson and Johnson and Luzanec America was acknowledged (Huncharek 2007), raising the issue of funding bias.

Langseth et al. published a comprehensive meta-analysis in 2008 of the risk of ovarian cancer associated with talc use. The combined OR was 1.35 (CI 1.26-1.46), and specifically 1.4 for population-based studies (CI 1.29-1.52), the less potentially biased type of study. Langseth et al. also noted that the risk of serous ovarian tumors in particular with talc use may be greater (Langseth 2008).

In 2016, Cramer published a retrospective case-control study that incorporated data from three enrollment phases (1992-1997, 1998-2002 and 2003-2008) and combined data from the Nurses' Health Study (Gates 2008) and data from participants in the Ovarian Cancer Association Consortium (OCAC, Terry 2013). The study found a statistically significant increased risk of invasive serous, invasive endometrioid and serous borderline ovarian tumors in women who were genital talc users, with the highest risk (OR=2.33 (CI 1.32-4.12) and OR=2.57 (CI 1.51-4.36) for pre- and postmenopausal women, respectively) with the greatest lifetime exposure, as defined by "talc-years," or number of applications per year multiplied by years of use. A dose-response was most prevalent for invasive serous carcinoma. This study is important as evidence supporting an association between talc and ovarian cancer as the authors analyzed case-control data collected over 16 years in 2,041 epithelial ovarian cancer cases and 2,100 age- and residence-matched controls. As the authors state, they "addressed issues related to definition of the exposure, bias and confounding, effect modification, histologic heterogeneity, and dose-response. Talc used regularly in the genital area was associated with a 33% increase in ovarian cancer risk overall." (Cramer 2016)

Berge et al. published another meta-analysis in 2018 that found a summary RR of 1.22 (CI 1.13-1.30). They found that the association between talc and ovarian cancer was stronger in case-control studies (RR 1.26, CI 1.17-1.35) than cohort studies (RR 1.02, CI 0.85-1.20). The limitations of the cohort studies are discussed above; limitations of case-control studies are recall bias and selection bias. Addressing the latter, Berge et al. found a higher summary risk estimate in hospital-based case-control studies compared to community-based case-control studies, but this difference was not statistically significant. Recall bias can be present in case-control studies, however, Berge et al. found the greatest association between genital talc use and serous carcinoma (RR 1.24, CI 1.15-

1.34). This would argue against recall bias, as participants would likely not know the categorization of epithelial ovarian tumors, nor the fact that invasive serous carcinoma has been shown to have the strongest association in the majority of studies.

Penninkilampi et al. published a meta-analysis in 2018 that found any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, CI 1.24-1.39). They found a dose-response effect with greater than 3600 lifetime applications (OR 1.42, CI 1.25-1.61) compared to less than 3600 lifetime applications (OR 1.32, CI 1.15-1.50). Similar to the Berge 2018 study, an association was found in the case-control studies (OR 1.35, CI 1.27-1.43) but not in the cohort studies (OR 1.06, CI 0.90-1.25). However, Penninkilampi et al. did find an association in cohort studies between talc use and invasive serous carcinoma (OR 1.25, CI 1.01-1.55). (Penninkilampi 2018)

XIV. POOLED STUDY REGARDING TALC USE AND OVARIAN CANCER:

The meta-analyses discussed above summarize previously published data and thus have increased statistical power for a more precise estimate of effect on talc in ovarian cancer risk (Cohn 2003). However, the strength of meta-analyses depends on the quality of the previously published data analysis. In comparison, a pooled study analyzes primary data from different studies/researchers. The Terry 2013 study is a retrospective pooled study from eight population-based case-control studies from OCAC. One advantage of pooled studies is the ability to include a large sample size; Terry et al. included 8,525 cases of ovarian, fallopian tube or perineal cancer and 9,859 controls. Some of the included OCAC studies had previously reported on powder use (Chang 1997, Cramer 1999, Merritt 2008, Moorman 2009, and Rosenblatt 2011), and according to Terry et al., three of these provided data for the pooled 2013 analysis that had not been included in the previous publications. The other three studies had not previously published their genital powder data (Goodman 2008, Lo-Ciganic 2012, Pike 2004). The pooled analysis showed an OR for genital talc use and epithelial ovarian cancer of 1.24 (95% CI 1.15-1.33) after adjustment for age, oral contraceptive use, tubal ligation, BMI and race/ethnicity (Terry 2013). This is consistent with the majority of meta-analyses and individual studies.

A strength of a pooled study versus a meta-analysis is that pooled studies have increased standardization. As an example, the Terry 2013 study excluded participants that data was not available on regarding tubal ligation, oral contraceptive duration, parity or height and weight. This adjusts for study-specific differences in confounding factors. A weakness of pooled studies is that they are limited by the methods of original data collection; for example, Terry et al. state "Limitations of our pooled analysis include differences in the wording of questions about genital powder use between studies and the retrospective nature of the exposure ascertainment." As Blettner (1999) stated, "Pooling decreases the variation caused by random error (increasing the sample size) but does not eliminate any bias (systemic errors)." In the 2013 Terry et al. study, classification between cases and controls differed between studies, as the women who were classified as genital powder users varied from "ever" use, "ever regular" use, to powder use for at least one year. However, Terry et al. conclude that if anything, this led to an underestimate of the true association for any given

study “[due to the fact that] exposure definitions are the same for cases and controls within each study, misclassification of genital powder exposure due to the question wording would be nondifferential....” (Terry 2013).

XV. ASBESTOS, TALCUM POWDER PRODUCTS, AND OVARIAN CANCER:

I have seen evidence that talcum powder products manufactured by Johnson & Johnson (J&J Baby Powder and Shower to Shower) contained and continue to contain asbestos, talc containing asbestiform fibers (e.g. talc occurring in a fibrous habit) heavy metals (such as cobalt, chromium, nickel) and fragrance chemicals (Longo et al. 2017 and 2018, Blount 1991, Blount Deposition 2018, Hopkins Deposition and Exhibit 2018, Pier Deposition and Exhibit 2018). Other than cobalt, which has been identified as a “possible” carcinogen, all of these constituents have been identified as known carcinogens by IARC (IARC 2012). It should be noted that National Institute for Occupational Safety and Health (NIOSH) has determined that “there is no safe level of asbestos exposure for any type of asbestos fiber” (NIOSH 1980). As part of my review and consideration of the evidence I have also reviewed Dr. Michael Crowley’s opinion that “fragrance chemicals in Johnson & Johnson talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products.” The presence of these constituents as part of the talcum powder product provides additional evidence of biological plausibility for talcum powder products to cause ovarian cancer.

Asbestos is a silicate mineral in polyfilamentous bundles. Other silicate minerals exist, such as talc, but asbestos is classified by its flexible fibers with small diameter and large length. The forms of asbestos are serpentine silicates (“sheet silicates”) such as chrysotile, and amphibole silicates (“chain silicates”) such as crocidolite, amosite, anthophyllite, actinolite, and tremolite (IARC Monograph). The carcinogenic properties of asbestos fibers depend on the length of the fiber (Stanton 1972) and its chemical composition, structure, and cell environment (Mossman 1998, Robledo 1999, IARC Monograph). Asbestos fiber surface reactivity with free radical generation has also been accepted as a mechanism of carcinogenesis (IARC Monograph). Asbestos-derived free radicals can lead to a variety of effects on cells including lipid peroxidation, DNA oxidation, TNF release, cell apoptosis, and increased uptake of asbestos fibers (Mossman 1983, Hobson 1990, Ghio 1998, Churg 1998, Gulumian 1999, Aust 1999, Upadhyay 2003, IARC Monograph). Asbestos fibers may directly cause the generation of ROS (IOM 2006) and indirectly cause ROS by inducing inflammation and macrophage activation (IARC Monograph).

It has long been generally accepted that asbestos exposure causes mesothelioma and lung cancer (Dement 1994, deKlerk 1996, Berry 2000). Approximately 125 million people around the world have been exposed to asbestos in work environments, and at least 90,000 people die each year from asbestos-related lung cancer, mesothelioma, or asbestosis (Burki 2009). The relationship between asbestos exposure and ovarian cancer had been less studied; however, in 2009, the IARC Monograph Working Group concluded that there is sufficient evidence to show that asbestos exposure can cause ovarian cancer (Straif 2009, IARC Monograph).

In the late 1960's, a suggested link between talc and ovarian cancer was made for the following reasons: first, talc powders were shown to contain asbestos (Cralley 1968); second, intraperitoneally placed asbestos in animals induced a proliferation of the ovarian mesothelial lining from one layer to multiple layers (Graham 1967). Of note, it was tremolite asbestos that was used by Graham, the same type of amphibole asbestos that is found in asbestos-contaminated talc. It is important to note that similar to talc being found on the ovarian surfaces of perineal talc users, asbestos fibers have been found in women whose household contacts worked with asbestos and in Norwegian paper and pulp workers (Heller 1996, Langseth 2007).

In 1972, Newhouse et al. published a study of the mortality of female asbestos workers and found at least 4 deaths due to ovarian cancer compared to an expected number of 0.6. During histological review of some of the pathology samples from these workers, there was evidence that another two deaths that had been registered as due to carcinomatosis were likely caused by ovarian cancer (Newhouse 1972).

Ten years later in 1982, Wignall et al. published a study that followed 535 women who were assembly workers that had direct crocidolite exposure during the manufacturing of military gas masks. The authors found 2 deaths due to ovarian cancer in women that were employed at the facility for less than 1 year, with a standardized mortality rate (SMR) of 1.77. Two ovarian cancer deaths occurred in women with a 1 year history of employment at the facility (SMR=2.11) and one ovarian cancer death in a woman with a 3 year history of employment (SMR=1.05). The authors noted that the expected number of deaths is low, making stable estimates of SMR difficult. However, the authors conclude that the "excess of deaths from carcinoma of the ovary was unexpected at the start of the study but appears to be related directly to exposure to asbestos" (Wignall 1982).

Also published in 1982 was a study by Acheson et al. that evaluated two groups of women exposed to asbestos who assembled gas masks in two separate facilities: 570 women at Blackburn (civilian respirators that contained chrysotile) and 757 women at Leyland (military respirators containing crocidolite). The study found a SMR in the crocidolite group for ovarian cancer of 2.75 (CI 1.42-4.81) and a SMR of 1.48 (CI 0.48-3.44) for the chrysotile group. The authors noted that the risk of ovarian cancer increased over time for up to 40 years post exposure (Acheson 1982).

A 1994 study by Rosler et al. examined mortality from ovarian cancer in a cohort of 616 women in Germany who had been occupationally exposed to asbestos. Although about 95% of asbestos used in Germany was chrysotile, the authors noted that they could not exclude a mixture containing crocidolite. Two deaths from ovarian cancer were observed, compared to an expected 1.8 (SMR 1.09, CI 0.13-3.95). (Rosler 1994).

In 1999, Germani et al. published a study of ovarian cancer mortality in 631 women workers in Italy who had been compensated for asbestosis. They found a total of nine ovarian cancer deaths (SMR 4.77, CI 2.18-9.04) which included four deaths in a subset of asbestos-textile workers (SMR 5.26, CI 1.43-13.47) and five deaths in the subset of asbestos cement workers (SMR 5.40, CI 1.75-12.61). (Germani 1999).

Also in 1999, Vasama-Neovonen et al. published a case-control study of ovarian cancer and occupational exposure in Finland. The Standardized Incidence Ratio (SIR) was 1.30 (CI 0.9-1.80) between ovarian cancer and “medium/high levels of asbestos,” and the SIR was 1.1 (CI 0.8-1.3) for “low levels of asbestos.” The SIR is obtained by dividing the observed number of cases of cancer by the expected number of cases in the general population. The type of asbestos fiber was not noted (Vasama-Neovonen 1999).

Again in 1999, Langseth et al. published a study of 4247 workers employed for at least one year between 1920 and 1993 in the Norwegian pulp and paper industry. 85% of them were paper or administration workers. The follow-up period for cancer was from 1953-1993. An excess risk of ovarian cancer was found (SIR = 1.50, CI 1.07-2.09). The SIR was highest among those younger than 55 years, and mostly among those working in paper departments. The type of asbestos fiber was not specified (Langseth 1999). Langseth et al. published a follow-up case-control study in 2004 that examined the association between asbestos exposure and ovarian cancer in this same cohort of female pulp and paper workers in Norway that had been found to have excess morbidity from ovarian cancer. In the case-control study, the odds ratio for occupational exposure to asbestos based on 46 cases of ovarian cancer was 2.02 (CI 0.72-5.66), although this was not statistically significant (Langseth 2004).

In 2000, Berry et al. published a study that evaluated the mortality of a cohort of over 5000 London asbestos factory workers, both men and women, who were followed for over 30 years since first asbestos exposure. The study classified exposure by degree (low, moderate and severe) and duration (2 years or less or more than 2 years). They assessed mortality by comparing the number of cohort deaths with the number of expected deaths in England and Wales based on sex, age and period. The study found that there was a significant increase of ovarian cancer in women with severe exposure for more than 2 years (SMR of 5.35) and an overall SMR for all exposure lengths of 2.53 (CI 1.16-4.8) (Berry 2000).

In 2005, Pira et al. published a cohort study of 1077 women with at least a one month history of employment between 1946 and 1984 at an asbestos-textile factory in Italy. A variety of asbestos types were used in this facility, including crocidolite. They followed up with the cohort in 1996. There were five deaths due to ovarian cancer with an overall SMR of 2.61 (CI 0.85-6.09), but there was a SMR of 5.73 for women with longer employment histories at the facility (greater than or equal to 10 years of employment). Among women with greater than or equal to 35 years since first employment exposure, the SMR was 5.37 (Pira 2005).

Also in 2005, Wilczynska et al. published a study of 1470 Polish asbestos cement factory workers with a follow-up period from 1945 to 1999 and a SMR of ovarian cancer among workers of 3.76 (CI 1.38-8.18). The type of asbestos fiber was not specified (Wilczynska 2005).

McDonald et al. published a study in 2006 that followed 567 people, mostly women, who had assembled gas masks in the Nottingham factory between 1940 and 1944 and showed

a SMR for ovarian cancer of 1.2 (CI 0.6-2.2). Gas masks assembled at this facility had filter pads that contained 20% crocidolite. As an aside, this study found that the first deaths due to mesothelioma happened a little more than 20 years after exposure, which is consistent with most other studies (McDonald 2006) and highlights the lengthy time interval between exposure and presentation of disease in asbestos-related mesothelioma.

In 2008 Reid et al. published a study of 2552 women and girls who lived in a Western Australia mining town between 1943 and 1992 where crocidolite asbestos was mined. They were not directly involved in mining but there was extensive environmental contamination of the town. They found a SMR for ovarian cancer of 1.52 (Reid 2008).

Reid et al. published a study in 2009 that followed the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos and added 416 women to the study that had worked in the Wittenoom crocidolite asbestos mines and mills. For the latter group, there wasn't an increased rate of ovarian cancer (SIR of 0.49, CI 0.01-2.74), but the authors noted that the "female Australian Blue Asbestos workers at Wittenoom mostly worked in the company offices, shop, and hotel. Their occupational exposure was unlikely to have been as high as that reported for women in the earlier cohorts, which may explain why no excess risk for ovarian cancer was observed" (Reid 2009).

Pukkala et al. published a study in 2009 on the incidence of ovarian cancer in women employed in various occupations in Denmark, Finland, Iceland, Norway and Sweden. One of the groups examined were plumbers, who are known to have occupational exposure to asbestos. Four ovarian cancers were found in this group of plumbers, with a Standardized Incidence Rate (SIR) of 3.33 (CI 0.91-8.52). Fiber type was not specified (Pukkala 2009).

Magnani et al. and Bertolotti et al. published studies in 2008 that followed the same cohort of former asbestos-cement workers who were employed at a facility in Casale Monferrato, Italy. A mix of crocidolite and chrysotile asbestos was used at this factory. They observed nine ovarian cancer deaths versus 4 expected (SMR of 2.27). In women who had 30 or more years of exposure, the SMR was 2.97 (Magnani 2008, Bertolotti 2008). Ferrante et al. published a study in 2007 that examined cancer mortality in the household contacts of men who worked at this facility; among women with exposure due to household contacts, there were 11 ovarian cancer deaths versus an expected 7.7, or SMR of 1.42 (CI 0.71-2.54). (Ferrante 2007).

I am aware of two meta-analyses, both published in 2011, that evaluated a link between asbestos and ovarian cancer. The first was published in 2011 by Reid et al. and analyzed fourteen cohort and two case-control studies of women with exposure to asbestos in their work environment. The majority of the cohort cases they evaluated are detailed above. The authors added a 2002 paper by Szeszenia-Dabrowska et al. that studied Polish women diagnosed with asbestosis and a 2004 paper by Mamo et al. that studied Turin asbestos textile factory workers (Szeszenia-Dabrowska 2002, Mamo 2004). The two case-control studies they evaluated were a 1992 study of Johns Hopkins patients by Rosenblatt et al. and a 2004 study

of Norwegian pulp and paper workers by Langseth et al., the same group of workers previously described above. Reid et al. concluded that although women “thought to have ovarian cancer” (not all cases of ovarian cancer were histologically reviewed and confirmed) had an increased rate if exposed to asbestos, the overall numbers were still small and further study was warranted as one misclassification could skew the data (Reid 2011).

The authors of the second 2011 meta-analysis, Camargo et al., included 18 studies. They did not include the 1992 Rosenblatt et al. study or the 2004 Langseth et al. study but added six others: a 1986 study of cement workers in the U.K. by Gardner et al., a 1989 study of friction material workers in the U.K. by Newhouse et al., a 2007 study of textile workers in the U.S. by Hein et al., a 2009 study of textile workers in the U.S. by Loomis et al., and two other 2009 studies by Harding et al. and Clin et al. The authors of this second meta-analysis came to a stronger conclusion that the findings were consistent with an association between asbestos exposure and an increased risk of ovarian cancer (Camargo 2011).

Considering the consistency of these studies, the Bradford Hill viewpoints (strength of association, consistency, biological plausibility, etc.) and the well-known carcinogenic properties of asbestos, it is my opinion to a reasonable degree of scientific certainty that asbestos exposure can cause ovarian cancer. Even disregarding the evidence that cosmetic talc is contaminated with asbestos, it is my opinion that talc is causally associated with ovarian cancer. However, to the extent that talcum powder products contain even small amounts of asbestos, the evidence of causation is even more compelling.

XVI. BRADFORD HILL ANALYSIS:

In 1965, Sir Austin Bradford Hill proposed nine viewpoints of a causal relationship: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment and analogy (Hill 1965). It is important to remember, however, as discussed at the beginning of this report, that Hill himself noted that none of these viewpoints of association – including the existence of a statistically significant relationship – is either necessary or sufficient to show causation. There are no “hard-and-fast rules”. Rather, the totality of the evidence must be weighed and considered. With that important command in mind, let us examine the evidence.

1. Strength of association:

Strength of association is often measured by the magnitude of the relative risk (CDC). All meta-analyses and pooled analyses have found a statistically significant increased risk of ovarian cancer in perineal talc users, with relative risks falling between 1 and 2. This is consistent with a causal relationship. Strength of association is higher for asbestos. There are a number of examples of causal relationships where the relative risk is less than 2.0 (e.g., second hand smoke and lung cancer, oral contraceptive use and breast cancer, radon exposure and lung cancer). It also is worth noting that small or moderate effects on the benefit side can have important clinical significance. For example, aspirin has been deemed “causal” of cardiovascular event reduction, based on multiple studies that reported a benefit between 20-30% reduction in cardiovascular events. The strength of this association, especially combined

with the consistency, weigh in favor of a cause-and-effect relationship between talc and ovarian cancer.

2. Consistency:

The statistically significant increased risk of ovarian cancer with talc use has been consistent in size across multiple studies, different populations, different investigators, multiple countries and over time. Hill stressed the importance of repetitive findings; no single study can prove or disprove causation due to possible inherent internal validity issues. The consistency of the increased risk of ovarian cancer (and in particular invasive serous carcinoma) with talc use found in numerous studies, in different countries, and after adjustments for confounding factors cannot be disregarded. There also is consistent evidence of an association between asbestos and ovarian cancer. This was a very important factor in my analysis.

3. Specificity:

Hill suggested that associations are more likely to be causal when they are specific, in other words, a particular substance causes a single disease. However, in the half-century experience has shown that this aspect of causation is not particularly important in the context of cancer. Few examples of specificity are found when it comes to cancer. Smoking is generally accepted to be a cause of lung cancer, yet smoking is also associated with COPD, heart disease, stroke, and asthma, amongst other diseases. In multiple studies, talc has been shown to be associated with epithelial ovarian cancer, with invasive serous ovarian cancer showing the strongest association. Asbestos is generally accepted to cause mesothelioma, lung cancer, and ovarian cancer. Asbestos is also generally accepted to cause asbestosis/pulmonary fibrosis, pleural inflammation and thickening. This was a less important factor in my analysis.

4. Temporality:

Exposure to a substance must precede onset of disease for it to be causal. The above-described case-control and cohort studies had the objective of assessing talc exposure that preceded the onset of disease. In cohort studies, the exposure data was obtained before any women were diagnosed with ovarian cancer. In the case-control studies, women with ovarian cancer reported exposures prior to their diagnosis and controls reported exposures in the same time frame. In many studies the exposures went back several decades, providing even more assurance that the temporality requirement is met. This was an important factor in my analysis.

5. Biological gradient:

A biologic gradient, or dose-response, refers to an increased exposure corresponding to an increased risk. In the case of talc exposure, dose-response would ideally include both frequency of use and duration of use, or “application years” (total lifetime applications) similar to “pack-years” used in the setting of smoking. However, application-years is much more difficult to assess than pack-years, since one cannot easily quantify the amount of talc

used during each perineal application (unlike in smoking, where one can easily count the number of cigarettes smoked to calculate pack-years). Yet, when studies have evaluated duration and frequency of perineal talc use, most have found an increased risk of ovarian cancer with increased exposure (Harlow 1992, Cramer 1999, Mills 2004, Merritt 2008, Wu 2009, Terry 2013, Penninkilampi 2018). In the case of asbestos and mesothelioma, a study published by Plato et al. in 2018 found “a significant, dose–response relationship between maximum intensity asbestos exposure and mesothelioma of the pleura and cumulative asbestos exposure with 30-, 40-, and 50-years lag time. Cumulative exposure to asbestos, even at low levels, entailed an increased risk of mesothelioma of the pleura, indicating that even short periods with cumulative doses <1.78 f-y/ml can increase the risk of mesothelioma. Time since first exposure did not show any sufficient dose–response relationship in the longest lag period (>50 years).” (Plato 2018)

While there is evidence of a dose response, this data is more equivocal because of the challenge in measuring and comparing the extent of talcum powder usage. The evidence of biological gradient for talcum powder products is therefore very difficult to study. The evidence of biological gradient supports cause and effect, but for the reasons noted, it is limited by difficulties in the measurement of exposure. This was an important factor in my analysis.

6. Plausibility:

In this context, plausibility means that an association can be explained by and is consistent with existing scientific knowledge and, in particular, that there is a biologically plausible explanation for the exposure (to talc) as a cause of ovarian cancer. Thus, plausibility is dependent upon the current state of scientific knowledge regarding a mechanism of disease. Hill noted plausibility is helpful but limited by current knowledge.

There is evidence that validates the biological plausibility of talc-related ovarian cancer. It is generally accepted that inflammation plays a role in carcinogenesis. Pelvic inflammatory disease and endometriosis are known risk factors for ovarian cancer, and they cause the release of inflammatory mediators. Talc is known to produce an inflammatory reaction, and is in fact used in clinical practice to induce inflammation in the pleura to treat patients with pneumothorax and pleural effusions. It has also been demonstrated that particles, including talc, can migrate proximally through the female genital tract and gain access to the perineum, ovaries, and fallopian tubes. Thus, it is plausible that talc can reach the ovaries and fallopian tubes and cause a proinflammatory reaction, including induction of cytokines and ROS that play a role in the onset of ovarian cancer. Other plausible mechanisms include a down-regulated immune response to MUC1, causing an immune tolerance of a MUC1-expressing cancer, and talc-induced macrophage TNF- α expression and subsequent ovarian tumorigenesis. The 2008 Gates study showed an association of talc and ovarian cancer in women with the GSTT1-null genotype (p-interaction=0.03), particularly in combination with the GSTM1-present genotype (p-interaction=0.03). It is thus plausible that women with a GSTT1-null phenotype are unable to eliminate talc as efficiently and are at increased risk of ovarian cancer. It is also highly plausible that asbestos in asbestos-tainted talc also releases cytokines and mutagenic ROS from inflammatory cells.

In the case of asbestos, fiber surface reactivity with free radical generation has been accepted as a mechanism of carcinogenesis (IARC Monograph). Asbestos-derived free radicals can lead to a variety of effects on cells including lipid peroxidation, DNA oxidation, TNF release, cell apoptosis, and increased uptake of asbestos fibers (Mossman 1983, Hobson 1990, Ghio 1998, Churg 1998, Gulumian 1999, Aust 1999, Upadhyay 2003, IARC Monograph). Asbestos fibers may directly cause the generation of ROS (IOM 2006) and indirectly cause ROS by inducing inflammation and macrophage activation (IARC Monograph). As noted above, the carcinogenicity of the other constituents of talc (cobalt, chromium, nickel, and fragrance ingredients) adds strength to biologic plausibility.

This biologic evidence, provides a biologically plausible explanation for the increased risk seen in the epidemiologic studies and is therefore a very strong factor in favor of a cause and effect relationship.

7. Coherence:

Coherence in this context means coherence between epidemiological and generally accepted knowledge of the disease in question. Numerous studies addressing talc use and ovarian cancer have indicated talc use increases ovarian cancer risk consistently. The coherence of the epidemiological evidence linking a risk of ovarian cancer with talc use, in tandem with biologically plausible mechanistic evidence discussed above, is striking and weighs heavily in support of causation.

8. Experiment:

Hill suggested that evidence drawn from experimental manipulation, particularly epidemiologic studies in which disease risk declines following an intervention or cessation of exposure, may lead to the strongest support for causal association. No studies exist that follow women after cessation of genital powder use and assess them specifically for a change in risk of ovarian cancer. The challenge of such a study is that it has been shown that talc-associated ovarian cancer takes years or decades before onset of disease. However, the Australian study performed by The Survey of Women's Health Study Group published in 1997 found that the risk of ovarian cancer was highest among women who were talc users and had not undergone surgical sterilization (RR=1.3, CI 1.1-1.6). (Green 1997). This indicates that tubal ligation or hysterectomy, by impeding the proximal migration of talc into the perineum to the ovaries and fallopian tubes, decreases the risk of talc-associated ovarian cancer, lending support to Hill's experiment aspect in the context of talc and ovarian cancer.

There are experimental studies in the literature that support a causal relationship between talc and ovarian cancer. Examples include studies that show increases in inflammatory markers following talc exposure (Allaire 1989, Genofre 2009, Arellano-Orden 2013). There is also evidence that talc causes neoplastic transformation in ovarian cells (Buz'Zard 2007) and that talc induces genotoxicity in mesothelial cells (Shukla 2009). Additionally, there is evidence that talc induces macrophage TNF- α expression (Cheng 2000), and macrophages that express TNF- α have been shown to promote ovarian tumorigenesis

(Hagemann 2006). Of note, invasive serous carcinomas commonly have p53 mutations and TNF- α induced chromosomal mutations have been shown to occur mostly in cells with p53 aberrations (Yan 2006).

It has long been generally accepted that asbestos exposure causes mesothelioma, ovarian cancer, and lung cancer (Dement 1994, deKlerk 1996, Berry 2000, IARC 2012). The experimental evidence was very important to my analysis.

9. Analogy:

Comparisons of similar associations can be used to determine plausibility. Hill suggested that when there is strong evidence of a causal relationship between a particular agent and a specific disease, researchers should be more accepting of weaker evidence that a similar agent may cause a similar disease. Analogy under the Bradford Hill viewpoints has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way (Susser 1991). In the case of talc and ovarian cancer, one can use the analogy of asbestos and mesothelioma. Both talc and asbestos are silicates, and asbestos causes an inflammatory and fibrosing reaction within the pleura, which is generally accepted to be the primary cause of mesothelioma years later. It is the inflammatory and fibrosing reaction caused by talc that has led to its common use in the treatment of pneumothorax and pleural effusions by injection into the pleural cavity. Similarly, in the case of asbestos, fiber surface reactivity with free radical generation has been accepted as a mechanism of carcinogenesis (IARC Monograph). The analogy evidence was somewhat important in my analysis.

XVII. CONCLUSION:

Based upon the totality of the evidence and consideration of the Bradford Hill viewpoints, which includes the high consistency and replication of the findings in the epidemiological studies, pathological, biological, and mechanistic evidence, it is my opinion, which I hold to a reasonable degree of scientific and medical certainty, that genital talcum powder exposure can cause ovarian cancer.

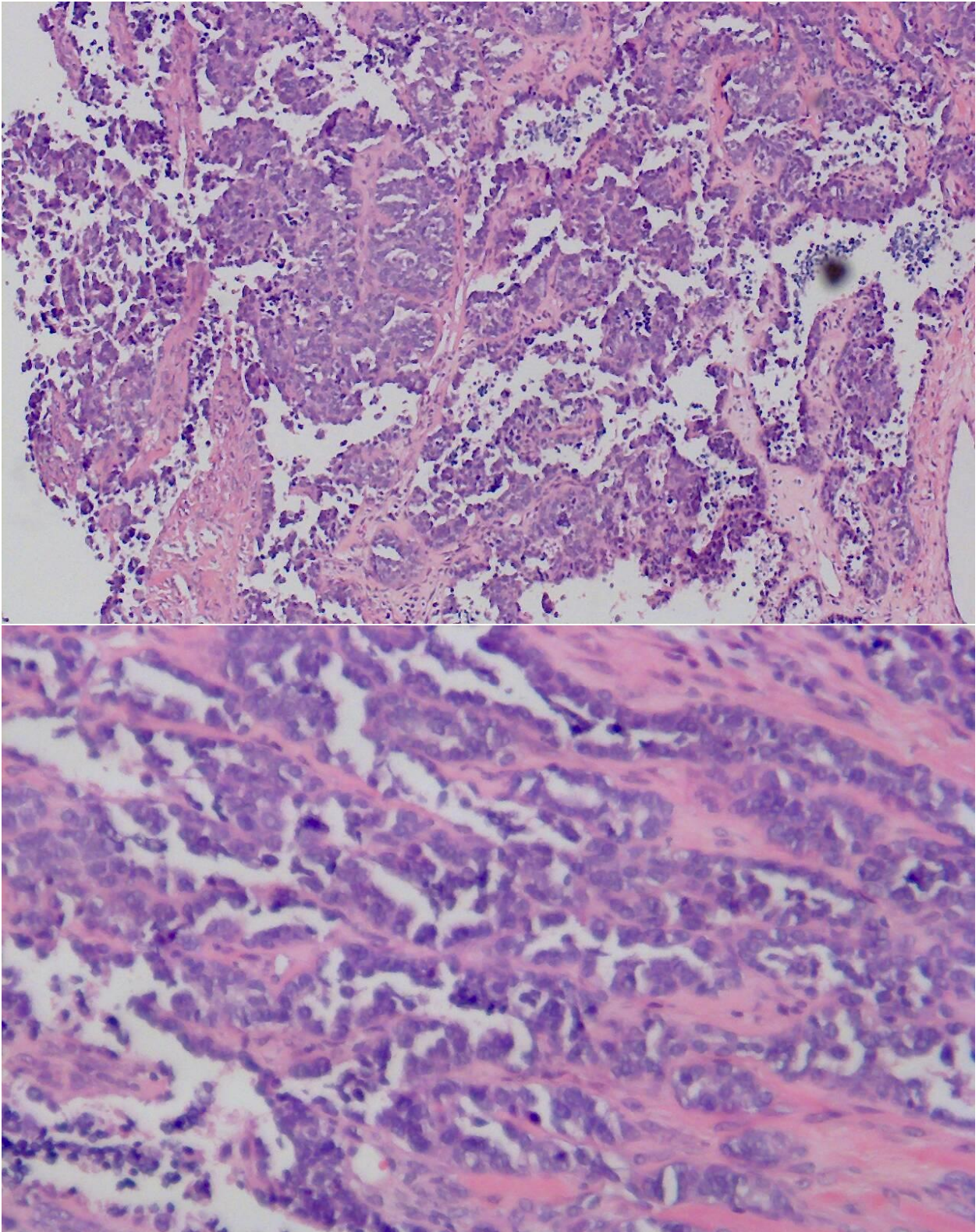


Figure 1. Ovarian invasive serous carcinoma.

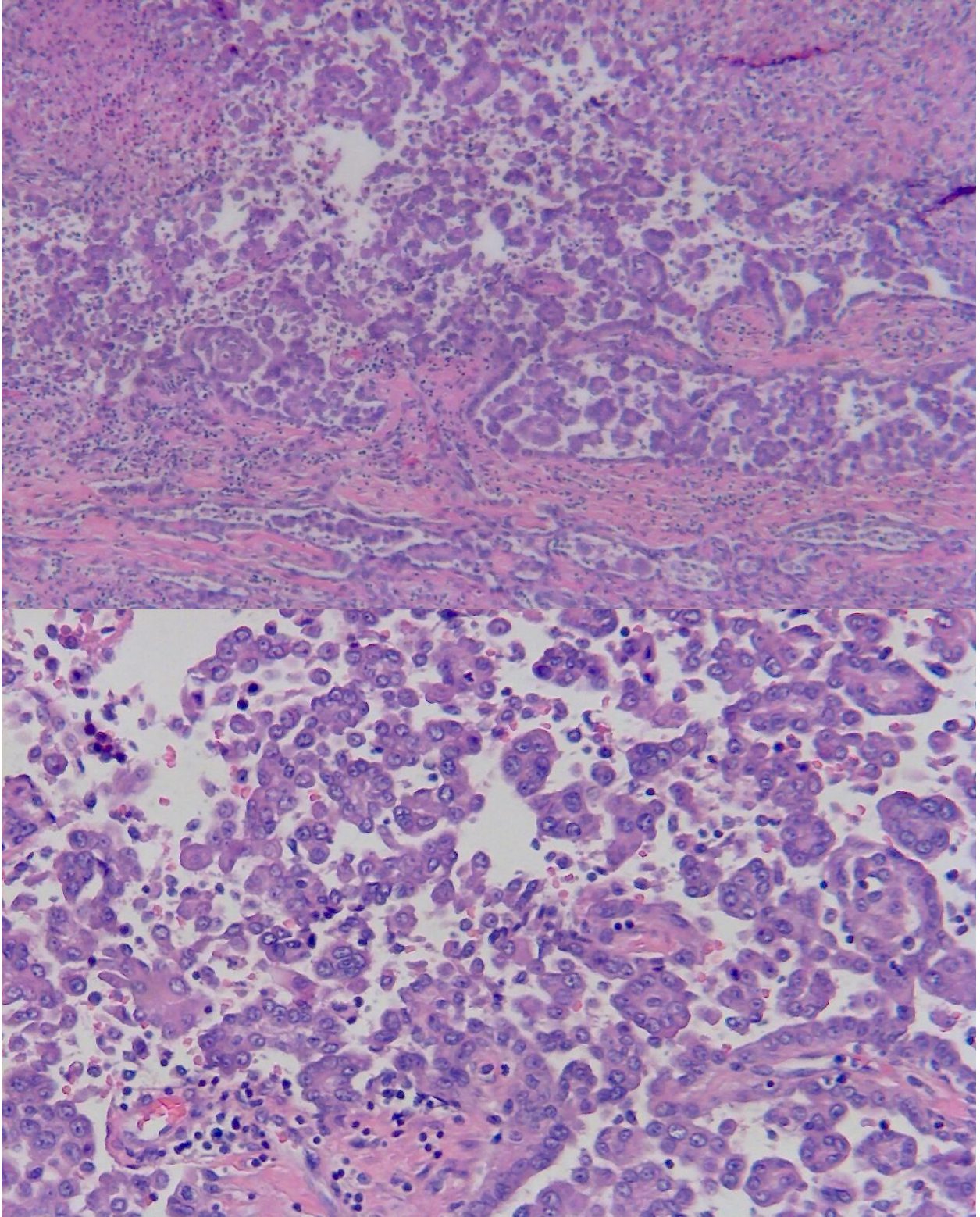


Figure 2. Mesothelioma. Notice the morphologic similarities to ovarian serous carcinoma (Fig 1).

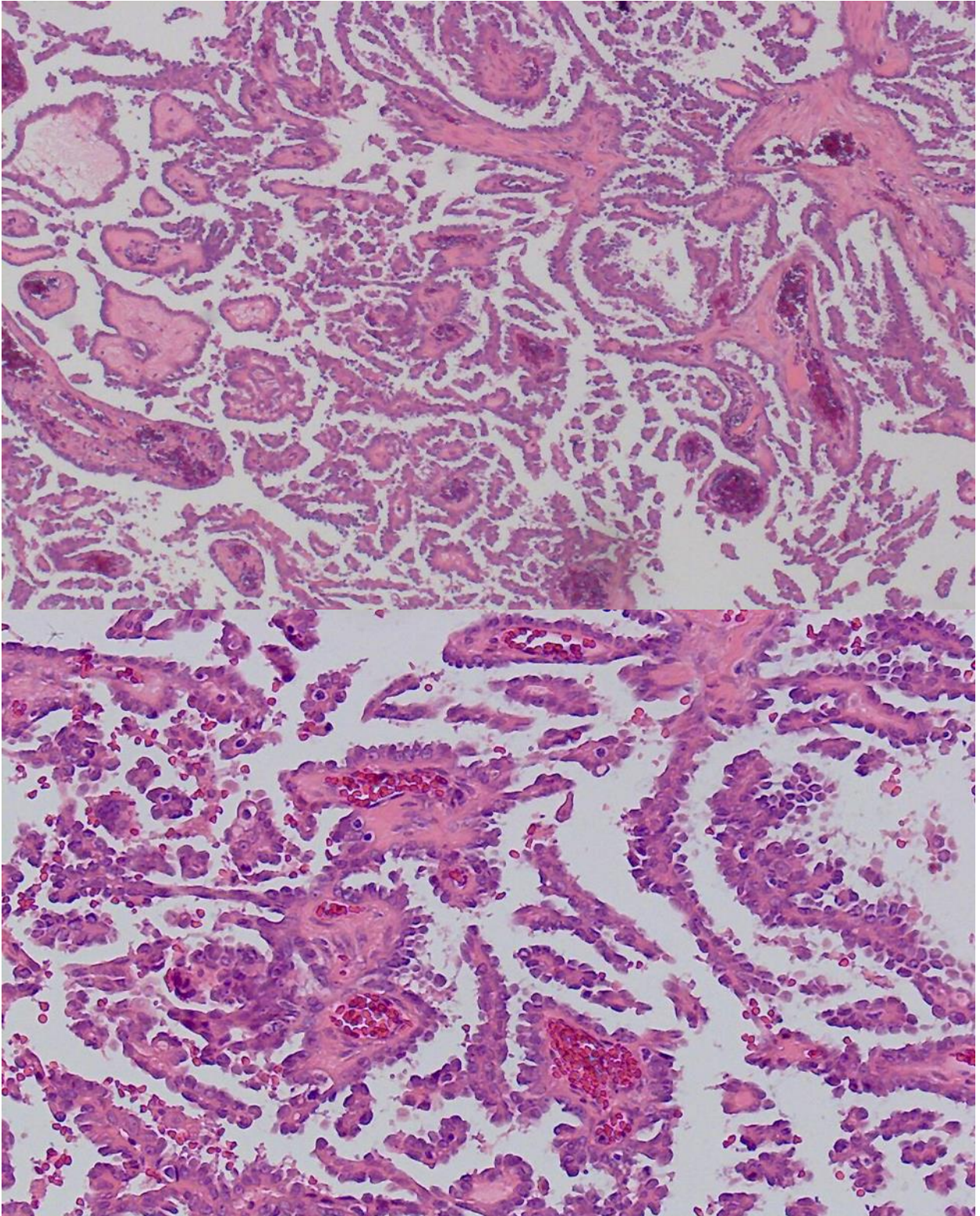


Figure 3. Ovarian serous borderline tumor.

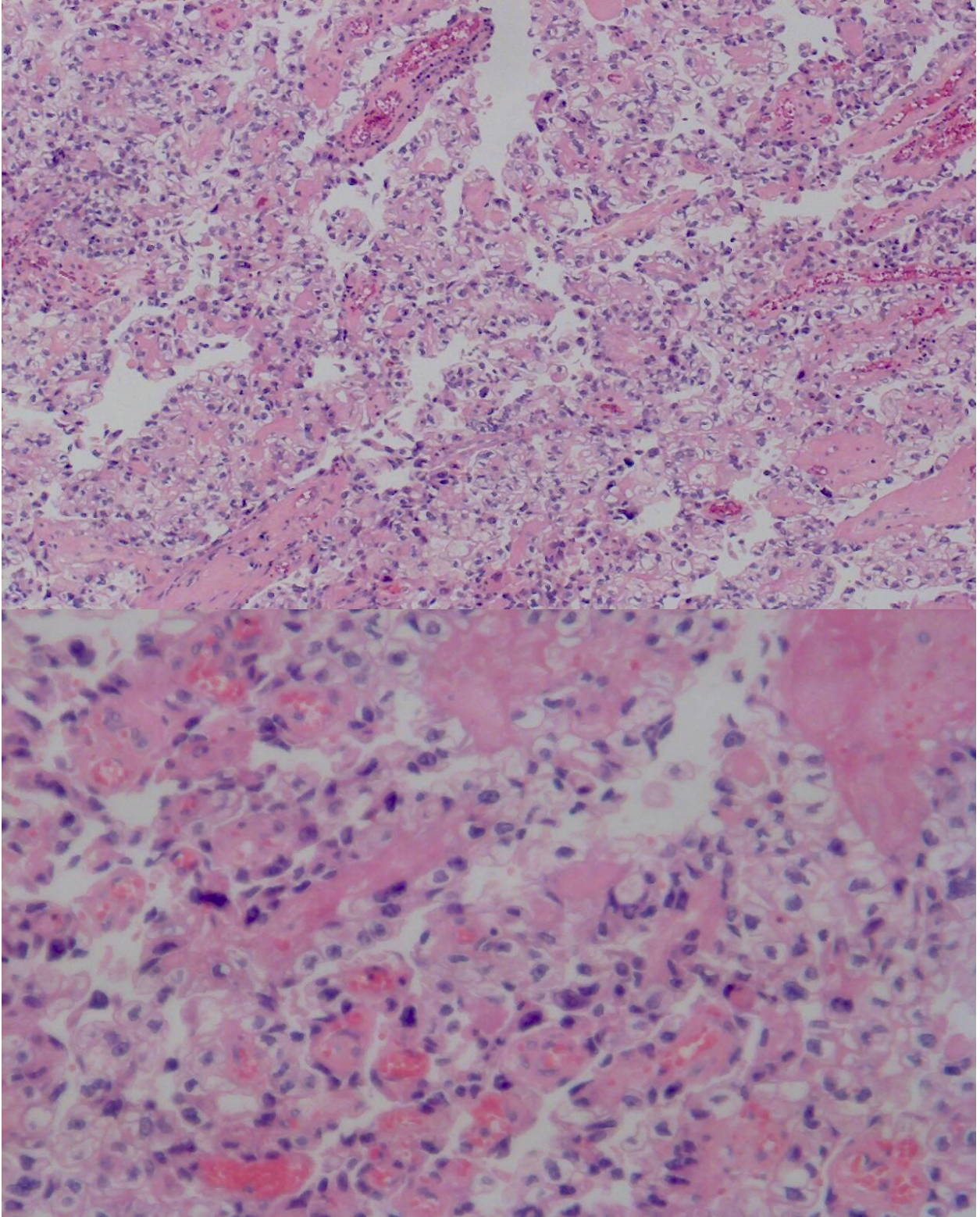


Figure 4. Ovarian clear cell carcinoma.

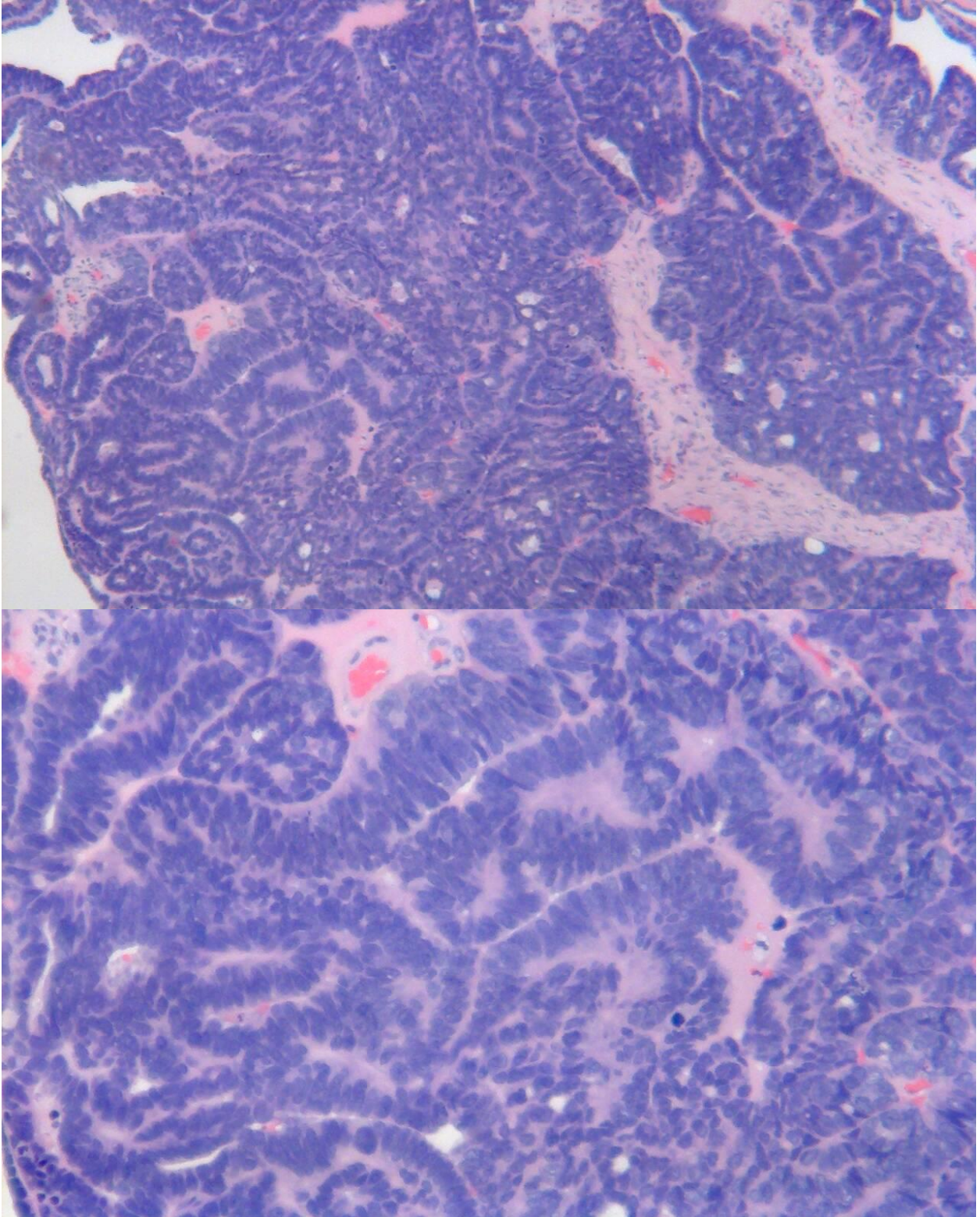


Figure 5. Ovarian endometrioid carcinoma.

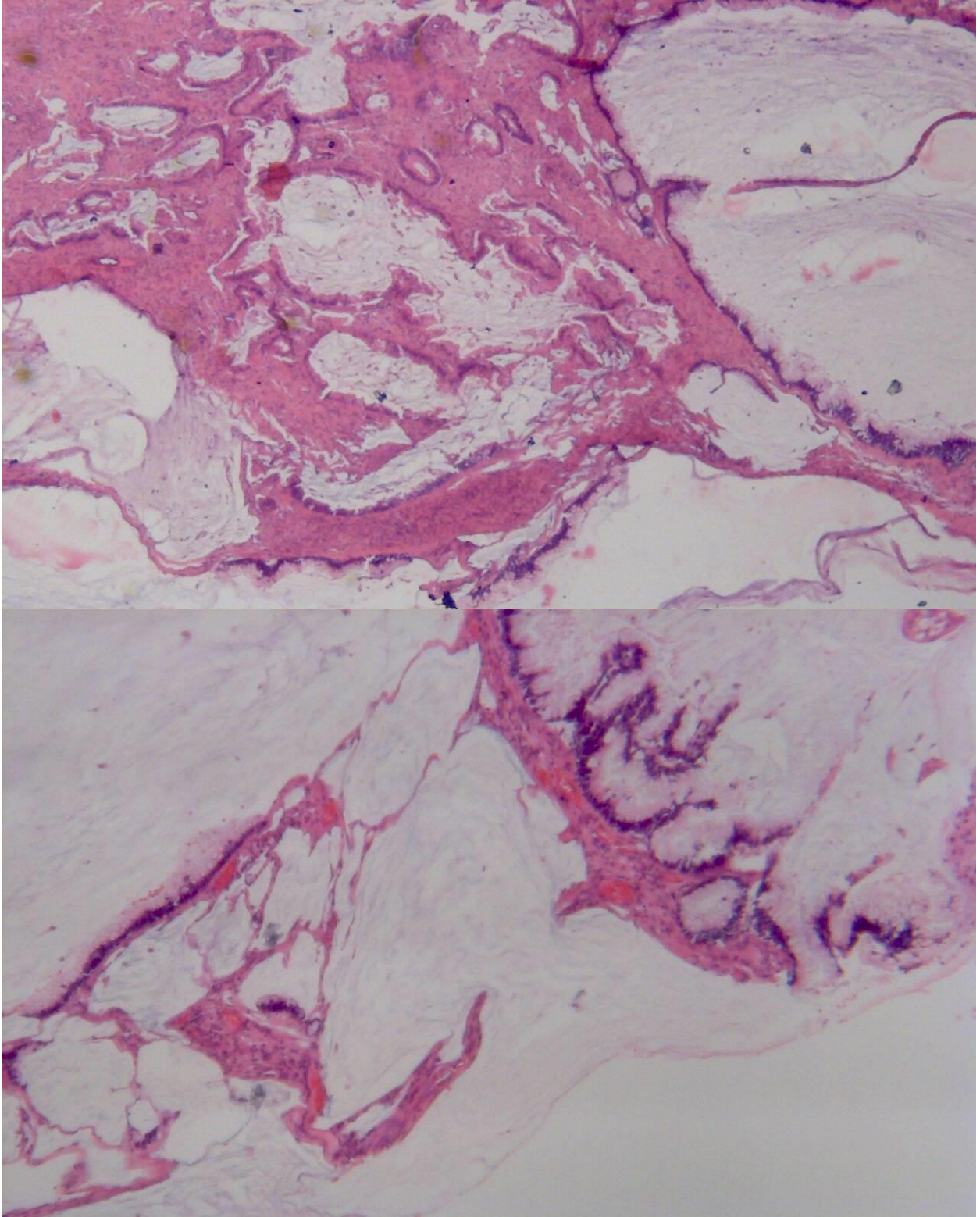


Figure 6. Ovarian mucinous carcinoma.

EXHIBIT A

CURRICULUM VITAE

Date prepared: January 2018

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Education:

1995	B.A.	Skidmore College Cum laude
2001	M.D.	The Ohio State University College of Medicine

Postdoctoral Training:

2001-2005	Resident	Pathology, AP/CP	Massachusetts General Hospital
2005-2007	Fellow	Robert E. Scully Fellow	Massachusetts General Hospital
		Cytopathology, Gynecologic and Perinatal Pathology	

Academic Appointments:

2001-2005	Clinical Instructor	Pathology	Harvard Medical School
2005-2007	Graduate Assistant	Pathology	Harvard Medical School
2007-2011	Instructor	Pathology	Harvard Medical School

Appointments at Hospitals/Affiliated Institutions

2007-2011	Staff Pathologist	Pathology	Beth Israel Deaconess
2007-2011	Staff Pathologist	Pathology	Beth Israel Deaconess-Needham
2011-Present	Staff Pathologist	Pathology	North Shore Medical Center
2011-Present	Staff Pathologist	Pathology	Newton-Wellesley Hospital
2011-Present	Clinical Affiliate	Pathology	Massachusetts General Hospital

Major Administrative Responsibilities:

2005	Chief Resident, Anatomic Pathology	Massachusetts General Hospital
2007-2011	Course Director, PA501.5 Elective	Harvard Medical School
2010-2011	Associate Director, Cytopathology Fellowship	BIDMC/Harvard
2012-2013	Hematology Laboratory Director NSMC	NSMC/Partners
2013-Present	Autopsy Director, North Shore Medical Center	NSMC/Partners

Major Committee Assignments:

2005-2007	Cytopathology	Junior Member	College of American Pathologists
2005	Path Residency Training Committee	Member	Massachusetts General Hospital
2005	Anatomic Path Quality Assurance	Member	Massachusetts General Hospital
2005	Anatomic Path Steering Committee	Member	Massachusetts General Hospital
2008-2011	Path Resident Selection Committee	Member	Beth Israel Deaconess
2009-2011	Path Residency Planning Committee	Member	Beth Israel Deaconess
2010	Pathology Scheduling Committee	Member	Beth Israel Deaconess
2010-2011	Anatomic Path Quality Assurance	Member	Beth Israel Deaconess

Professional Societies:

1997 – 2001	American Medical Student Association	Member
2001 – Present	Massachusetts Medical Society	Member
2003 – Present	United States and Canadian Academy of Pathology	Member
2005 - Present	College of American Pathologists	Member

Awards and Honors:

1994	Charlotte W. Fahey Prize in Chemistry, Skidmore College
1994	Skidmore College Periclean Honor Society
1995	Phi Beta Kappa, Skidmore College
1995	Cum Laude with Department Honors, Skidmore College
2000	Honors in Pediatric Hematology and Oncology 4th Year Clerkship
2000	Letter of Commendation, Surgery Third Year Clerkship
2000	Letter of Commendation, Neurology Third Year Clerkship
2001	Honors in Anatomic and Clinical Pathology Fourth Year Elective
2001	Honors in Individual Studies in Pathology Fourth Year Elective
2016	Partners in Excellence Team Award

Teaching of Students:

Harvard Medical School Courses:

2007-2009	Respiratory Pathophysiology
2 nd Year Medical Students	Lab Instructor Three 2 hour sessions, one week

2007-2009 2 nd Year Medical Students	Cardiovascular Pathophysiology Lab Instructor	Three 2 hour sessions, one week
2007-2011 3 rd Year Medical Students	Core Surgery Clerkship Pathology Coordinator	One hour lecture/3 months
2009-2011 3 rd Year Medical Students	Principal Clinical Experience Mentor	Two hour session per week
2009-2011 3 rd Year Medical Students	Principal Clinical Experience – Pathology Elective Mentor	Minimum 2 hour session/month

Formal Teaching of Residents:

2007 All pathology residents	Respiratory Cytology Beth Israel Deaconess	One hour lecture
2007-2011 Pathology residents rotating through Cytology	Respiratory Cytology	Quarterly 1 hr microscope session
2008-2011 All pathology residents	Fine Needle Aspiration Techniques Beth Israel Deaconess	One hour lecture
2008-2011 All pathology residents	Histologic and Cytologic Correlation of Cervical Lesions Beth Israel Deaconess	One hour lecture

Clinical Supervisory and Training Responsibilities:

2007-2011 Core Surgery Clerkship, Pathology Elective BIDMC 2 students/month

Local Invited Presentations:

2005 Cytology/Histology Correlation Clinical Pathology Technician Lecture Series
Department of Pathology, Massachusetts General Hospital

2008 Respiratory Cytology Cytopathology Lecture Series
Department of Pathology, Brigham and Women's Hospital

Current Licensure and Certification:

2005 Full License, Massachusetts

2008 Board certified, Anatomic and Clinical Pathology

2008 Board certified, Cytopathology

Practice Activities:

Surgical Pathology, Cytopathology, Autopsy	North Shore Medical Center
Surgical Pathology, Cytopathology	MGH Ambulatory Care Center
Cytopathology	Massachusetts General Hospital
Clinical Pathology	Newton-Wellesley Hospital

Peer-Reviewed Publications:

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EXHIBIT B

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Board Certified in Anatomic and Clinical Pathology, and Cytopathology

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